Neuroimaging studies in pediatric obsessive compulsive disorder
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Chapter 1

Introduction
Introduction

Joe Wells was a 16 year old boy when he wrote his book “Touch and go Joe. An adolescent’s experience of OCD” (313). He describes his life with an obsessive compulsive disorder (OCD). It started when he was 9. While his younger sister, Emma, 6, was playing in the garden, Joe would be standing at the bathroom sink, struggling to turn the tap off with his wrist. “I felt I had to avoid touching the tap in case somebody with dirty hands had touched it,” he says. “It might be the tenth time I’d washed my hands that day but I knew it wouldn’t be the last, even though my hands were red and sore. I’d become obsessed with fears of poisoning.”

More dangers loomed: from car exhaust fumes to bacteria and even wallpaper solvents. “I was paranoid about touching door handles because of germs. Any of them could be the end of me. My home had become a terrifying place.” The more Joe tried to push a worrying thought out of his mind, the more it would force its way in. “I felt I was a freak. Or going mad. Either way, I didn’t want anyone to know. Even Mum and Dad.”

At 11, Joe’s family moved house and losing familiar surroundings increased his worries. “I developed a huge fear that if I sinned, I’d die. A lot of stuff we were taught in Sunday school was very heavy. Fear of God became part of my OCD. I had to keep repeating: ‘I do believe in God and I do accept him in my life.’ I was like an anxious monk.” Worry then focused around his negative thoughts. “My fear was that having thoughts was the same as making them happen. If an unwanted thought came into my head, such as I wanted someone to die, I immediately had to make myself have the opposite thought to cancel it out,” he says. “To reinforce the effect, I’d have to lean my head in whichever direction I thought they were. If I didn’t know, I’d have to lean my head in four different directions and repeat that cancelling-out thought four times. If something interrupted, I’d have to begin again.”

By 12, Joe was terrified that his soul would be stolen. To guard against that he performed complicated tapping sequences. “I needed to tap an object a certain number of times or my soul would be taken away. If I lost count, I’d have to start again. I was tapping thousands of times a day.” That summer Joe and his family holidayed in Corfu. “Because it was a strange place, my stress levels rocketed. The rituals became completely unmanageable.” He remembers tussling with his parents in a restaurant. “I was in the middle of tapping a plate. They were trying to take it away, I was pulling it back. They couldn’t understand why I was so upset and angry.” By then he had developed stepping routines to prevent his soul being stolen. “But because I had to step on all the different road surfaces, it made me sway as I walked.” At one point OCD thoughts were so overwhelming that he could hardly walk. “I began to meander as if drunk. If I linked arms with one of my parents, I could walk straight, but I’d still be stamping my feet or taking exaggerated strides. Unsurprisingly, my parents didn’t want to walk with me.”
The problem couldn’t stay hidden. “Luckily, Mum had been lent a book by a friend, which described OCD. Mum said that it sounded like what I had. I didn’t argue. Stopping those thoughts had become as impossible as stopping the Niagara Falls.” Joe’s GP referred him to the Hampshire NHS family-therapy team who diagnosed OCD. “Having a label helped,” he says. “I wasn’t a freak. This was a proper illness.” He was referred to a clinical psychologist, Alison Wallis, for cognitive behavioral therapy to challenge the OCD beliefs. “She’d ask me to give evidence for and against the ideas behind the compulsions, and for the specific fear of losing my soul.” The therapy seemed to be helping, then adolescence kicked in. “I was like Harry Enfield’s teen character Kevin, Joe Wells and OCD molded into one. I had constant arguments with my parents. Depression and OCD was a terrible combination.” At that point he was prescribed selective serotonin re-uptake inhibitors (SSRIs), a medication to treat depression and anxiety. “I began to feel more confident. I started arranging to go out with friends. I found the courage to tell people about my disorder. With Mum’s encouragement, it developed into a book.”

After eight years, Joe finally feels free of OCD. “I started coming off the medication last June and stopped completely at Christmas. Occasionally, I’ll still have ‘soul theft’ thoughts when I’m stressed, but not so much that it disrupts my life. I’m still able to think rationally. It’s wonderful to get my life back. Now that I’ve overcome OCD, I feel that I can overcome anything.” (319)

Joe Wells story illustrates very well what happens with children with OCD, the effect of development (“then adolescence kicked in”) and how treatment makes a difference. For decades scientist and therapist are struggling to understand this strange disorder. How can fears become so overwhelming, how can thoughts become so uncontrollable and resulting in compulsive behavior which rules some bodies entire life? What happens in the brain of these children? What is going wrong and how to repair it?

The focus of this thesis is on what happens in the brain when a child has an obsessive compulsive disorder and how treatment can influence brain anatomy and functioning. After a more general introduction with an emphasis on neurobiological factors we will give the outline of this thesis.

Obsessive compulsive disorder is defined as recurrent obsessions and compulsions that are time consuming or cause marked distress or significant impairment in daily functions(5). The DSM-IV further states that obsessions are recurrent and intrusive thoughts, ideas, images, or impulses that causes marked anxiety and distress. Common obsessions in adults and children include preoccupations with contamination, harm to self or others, and symmetry, as well as fear that a bad outcome will occur if a ritual is not completed in just the right way. In addition, compulsions are defined as repetitive behaviors or mental acts
that prevent or reduce anxiety caused by an obsession. Common compulsions in adults and children include washing, checking, and ordering rituals. A typical compulsion of children is compulsive questioning, parents have to give ritualistic answers which can be very time consuming (92). About one third of adults and 40% of children diagnosed with OCD deny that compulsions are driven by obsessive thoughts (111). Adult patients with OCD will often recognize that their obsessions are irrational but, irrespective of this insight, will continue to experience anxiety and engage in compulsions. Children and adolescents more often have limited insight and do not experience their symptoms as irrational.

OCD is recognized among the ten leading causes of disabilities in the world (318). Having a lifetime diagnosis of OCD is associated with an increased likelihood of developing depression, alcohol abuse, drug abuse, phobic disorders, and antisocial personality disorder. About half of the patients start with OCD symptoms before adulthood.

A bimodal distribution of age of onset has been suggested with an early onset peak between 6-15 year and a late onset peak between 20-29 years (121). Early onset OCD patients compared to late onset patients are more likely to be a man (gender ratio 2:1), have more often co morbid tic’s, separation anxiety disorder and show an association with disruptive behavior disorders (ADHD and oppositional defiant disorder) and other specific and pervasive developmental disorders, and have more often a family history of OCD and tic disorders (70). In this thesis we will talk about pediatric OCD defined as patients with OCD up to 18 years. These patients are by definition early onset patients. Whether early onset OCD is a distinct subtype or a precursor of adult onset OCD is not yet clear.

The prevalence of pediatric and adult OCD differs among studies between 0.06% and 4% (95;121;244;332). Because we do not see a rising cumulative prevalence in adulthood, it has been suggested that some children and adolescents with OCD either become subsyndromal or remit over time (271). Persistence rates over time have been found of 40 to 60% with earlier age of onset, duration of illness and outpatient versus inpatient status as predictors of persistence of OCD symptoms, co morbid psychiatric illness and poor initial treatment response were poor prognostic factors (271).

Co morbidities rates in pediatric OCD are in general high; in a study of the National Institutes of Mental Health (NIMH) in the USA a childhood onset OCD cohort revealed that only 26% of patients had OCD as a single diagnosis (7). The most common co morbidities in children are ADHD (34%-51%), major depression (33%-39%), tics (26%), specific developmental disabilities (24%), Tourette syndrome (18%-25%), oppositional defiant disorder (17%-51%), and overanxious disorder (16%) (25-27). In the NIMH cohort, rates were also increased relative to a control group with simple phobias (17%), adjustment
disorder with depressed mood (13%), oppositional disorder (11%), conduct disorder (7%), separation anxiety disorder (7%), and enuresis/encopresis (4%)(146).

Some authors suggest that OCD patients with co-morbid tic disorder are a subgroup of OCD with a differential etiology and treatment outcome and that “tic-disorder related” should be a specifier for OCD in DSM V (140-142;253).

Another way of subtyping OCD is looking at symptom dimensions. Several authors found a four factor model of symptom dimensions in adult and pediatric OCD (168;169;272;273) with a factor for aggressive, sexual, religious or somatic obsessions and checking compulsions, a factor for symmetry, ordering, counting and repeating obsessions and compulsions, a factor for contamination obsessions and cleaning compulsions and finally a factor for hoarding. These dimensions were associated with distinct patterns of comorbidity, genetic transmission, neural substrates, and treatment response and were stable over time. This subdivision has still a substantial overlap and OCD is not seen as multiple disorders but as a spectrum of potentially overlapping dimensions that can co-occur in any given patient(169).

Twin studies has shown that genetic factors play an important role in OCD in which in children obsessive compulsive symptoms show a heritability of 45-65%, whereas adults show a heritability of 27-47% (303). Results of gene studies have been mixed and no single gene, especially not in serotenergic and dopaminergic pathways, has been replicated within OCD populations with the exception of the glutamergic transporter gene **SLC1A1** on 9p24(306).

Treatment of choice for pediatric OCD is cognitive behavioral therapy (CBT)(161). The main objectives of CBT are identifying the triggers of obsessions and compulsions and designing personalized exposure and response prevention (ERP) strategies that can be practiced outside the therapy sessions. In addition several cognitive strategies can be explored to challenge the distorted cognitions, e.g. discussions and experiments to demonstrate the effects of thought suppression and neutralization, modification of inflated risk and responsibility appraisals using pie charts and risk assessment analyses. The most widely used manual for CBT in children and adolescents with OCD is from March et al (163). This protocol places OCD within a neurobehavioral framework, and therapy consists of three phases: (1) psycho education, anxiety management training (AMT), and cognitive therapy; (2) exposure and response prevention (ERP) (in vivo or imaginable and as weekly homework assignments); and (3) relapse prevention and award ceremony. De Haan and
Wolters (93) wrote a manual within the Dutch context with comparable ingredients and extended the manual with a book with homework assignments for the patient (316). During psycho education the patient and his family are explained about OCD, its causes, prevalence, maintaining factors, prognosis and treatment options. OCD is framed as an anxiety disorder resulting from misattributing of normal but unpleasant intrusive thoughts. Anxiety management techniques like relaxation training can be used to tolerate stressful situations. Registration of the obsessions and compulsions is made in order to make a hierarchy. Exposure is started with the least distressing situation and gradually progressing through the more feared situations without conducting the compulsions. The most commonly proposed mechanism for the effectiveness of ERP is that over prolonged exposure to feared stimuli, physiological components of anxiety are corrected by autonomic habituation. In addition, successful completion of exposure is thought to facilitate the development and storage of corrective cognitive information with respect to the feared situation or stimuli, as children learn that the feared consequences of not ritualizing are not going to occur (293). There is some discussion to what extent cognitive techniques as risk re-appraisal, responsibility re-appraisal, and discussion of thought suppression contribute to the effectiveness of CBT. BT with only ERP has been shown to result in comparable outcome as CBT (24). CBT has been effective on an individual basis, in groups (96), in family based settings (17) and in intensive day treatment (274) even a telephone based CBT (293) has proven to be effective. A meta analysis of CBT in pediatric OCD showed an pooled effect size of 1.45 whereas medication showed a overall effect size of 0.48 (310).

A large multi-site study investigating CBT, SSRI medication, their combination and placebo revealed that the combination (CBT and medication) was superior to either treatment alone and all active treatments were superior to placebo (213). Medication treatment in general consist of SSRI or clomipramine (161). In a meta analysis of all medications in pediatric OCD (73) SSRI's showed a modest effect on OCD symptomatology superior to placebo. Clomipramine showed to be superior to SSRI's (162).

The neurobiology of OCD

**Neuroanatomy**

The fronto striatal circuit is generally recognized as the neural basis of the obsessive compulsive disorder (10; 156; 232; 252). Parallel circuits between the prefrontal cortex, the striatum, basal ganglia and the thalamus and a closing loop back to the cortex has been described (3). There is no consensus in the literature about the number of loops, but most authors describe five parallel loops targeting the following areas: The supplementary motor area, the frontal eye fields, the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC). The latter three loops are described in
relationship to OCD but also to other psychiatric disorders like attention deficit disorder (ADHD), autism, depression, schizophrenia and Tourette disorder (28). These loops have been confirmed in diffusion tensor studies in humans (145).

The DLPFC projects at the dorsolateral head of the nucleus caudate, the dorsolateral globus pallidus interna, subthalamic nucleus, globus pallidus externa and substantia nigra pars reticulare to the ventral anterior and dorsomedial thalamic nuclei. The OFC projects at a more ventromedial part of the nucleus caudate and dorsomedial globus pallidus, returning via the ventral anterior and medial dorsal thalamic nuclei. The ACC projects to the ventral striatum, nucleus accumbens and parts of the ventromedial caudate and putamen and returns via the dorsomedial thalamic nucleus (Figure 1).

The striatum and basal ganglia have a direct and an indirect pathway through which they project to the thalamus: The direct pathway projects from the striatum to the globus pallidus interna/substantia nigra pars reticulare to the thalamus whereas the indirect pathway projects via the globus pallidus externa through the subthalamic nucleus at the globus pallidus interna to the thalamus. The direct pathway has an excitatory net effect and the indirect pathway an inhibitory effect. These two pathways keep the outcome in balance.

The DLPFC circuit closes the gap between sensation and behavior, integrating with long-term memory structures in the inferotemporal cortex (visual) and the parietal cortex (spatial and praxic) and providing working memory, a buffer for response schemata’s and action plans, and a basis for the establishment of a prospective or preparatory set. The DLPFC mediates executive functions like planning, organization, shifting or maintaining set and focus of attention. The DLPFC mediates the “how to do it?” of an action. The OFC circuit is largely responsible for the behavioral significance of stimuli: The recognition of reinforcing stimuli, stimulus-reinforcer learning, coding for changes in reinforcement contingencies and emotionality, personality and autonomic functions. The OFC mediates the “What to do, or what not to do?” The ACC circuit is particularly active during demanding situations that require divided attention, conflict resolution, error detection, response monitoring and the initiation and maintenance of appropriate and ongoing behaviors. The ACC mediates the “When to do it?” especially the motivational aspect (28).

The striatum and basal ganglia have several important functions: Filtering, selecting and inhibiting action sequences, optimizing (scaling) the pattern of activity to reach target, chunking repertoires, binding or synchronizing cortical activity, to achieve coherent responding.

In OCD it is hypothesized that a hyperactivity of the ventral and medial prefrontal cortex (OFC and ACC) and dysfunctional dorsal lateral prefrontal cortex result in an overload of the
striatum(10;170). Other authors emphasize a dysbalance of the direct and indirect pathway, with hyperactivity in the ventral direct pathways which results in a positive feedback loop in which obsessive thoughts become trapped(250) (See also figure 1). Some authors suggest a possible additional role for the amygdala and hippocampus in mediating the arousal and anxiety state of OCD patients(30;220).

Figure 1. The fronto striatal circuits

In OCD a hyperactivity of the ventral circuits (OFC and ACC) and a dysfunction of the DLPFC circuit are hypothesized to underlie pathology resulting in a shortcut of input from the prefrontal areas back to the frontal areas. Grey symbols represent the situation in OCD.

Outside the frontostriatal circuit is the parietal cortex, often in combination with the DLPFC, and the insular cortex, often in combination with medial and ventral PFC and ACC, linked to OCD symptomatology (176). The parietal cortex play an important role in attentional, spatio-temporal tasks and the sensory control of action(49). The insular cortex is associated
with somato sensory integration, interoceptive awareness and emotion regulation (130). In OCD the insula has been associated with disgust reactions(207).

In adolescence the brain and especially the prefrontal areas are still in development. Brain development parallels cognitive milestones. First sensory and motor systems mature, which is reflected in development of somato sensory and occipital areas, then basal language skills and spatial attention develop, associated with maturation of medial temporal and parietal areas, where as higher order functions which integrate primary sensorimotor processes and modulate basic attention and language processes, associated with prefrontal and lateral temporal areas, seem to mature last. Especially the DLPFC is among the areas where maturation continues into early adulthood. During normal development striatal structures mature earlier than prefrontal regions(42;85;164;268). These processes allow for fine-tuning and strengthening of connections between prefrontal and subcortical regions leading to greater cognitive control (44).

The neurodevelopmental process of maturation, reflected in the U shaped pattern of neurodevelopment of gray matter found in several longitudinal developmental MRI studies (85;268;292), seems to reflect processes like pruning of redundant synaptic connections. Whereas with matter seems to have a more linear development reflecting the myelination of axons during development. Individual sub regions follow temporally distinct maturational trajectories in which higher-order association areas mature only after lower-order sensorimotor regions have matured (85). In normal development adolescents are therefore biased by elevated sub cortical limbic responses to motivational and emotional cues relative to less mature cortical recruitment, compared to children, in whom this front limbic circuitry is still developing, and compared to adults, in whom these systems are fully mature. With development and experience, the functional connectivity between these regions is strengthened and provides a mechanism for top-down modulation of the sub cortical systems(41). These findings are especially relevant for circuits that encompass both cortical and subcortical regions, such as those likely to be involved in OCD. Alterations in timing or degree of maturation may underlie neurodevelopmental pathology. It is hypothesized that a developmentally mediated network dysplasia underlie pediatric OCD, more specific an abnormality in postnatal pruning involving an exaggeration of pruning or reduction of neural brain elements in striatum and a reduction in pruning in ventral PFC. Alternatively, there may be a dysplastic process involving hypoplasia of striatal structures and a hyperplasia of VPFC(232). This could lead to neuroanatomical, neurochemical and functional abnormalities.
Outline of this thesis

In this thesis we will investigate the neurobiological basis of pediatric obsessive compulsive disorder.

The studies in this thesis aim at answering three main questions:

1. What are the differences in brain functioning between pediatric OCD patients and healthy controls?
2. What is the mechanism of change at a neurobiological level during cognitive behavioral therapy?
3. What are developmental aspects of brain functioning in pediatric OCD patients?

Investigating pediatric patients has the advantage of investigating these patients relative early at the onset of their disorder without confounding factors as treatment response, medication and the effect of the disorder itself on the developing brain. To address the above questions we investigated a sample of 29 pediatric OCD patients which we recruited from our specialist center for pediatric OCD. These patients were part of a larger study which investigates (neuro) psychological and biological mechanisms of change during cognitive behavioral treatment for pediatric OCD.

For each patient a healthy control was recruited matched on age and gender.

All patients were treated with 16 weekly sessions of protocolized cognitive behavioral therapy supervised by the authors of the manual.

Before and after this CBT patients were scanned with three different MRI techniques. Controls were scanned twice with the same scanning protocol and at the same time interval.

The MRI techniques were a structural T1 scan to detect regional gray and white matter volume differences, a diffusion tensor imaging (DTI) technique to detect differences in white matter tracts and connectivity and functional MRI (fMRI) to detect differences in activation patterns during cognitive tasks. For the fMRI we aimed to probe the three different parallel circuits of the fronto striatal system. We explored a planning paradigm, the tower of London, to probe the dorsolateral circuit, an interference task, the flanker, to probe the ACC circuit, and a selective attention task, the dot-probe, to probe ventral fronto striatal and limbic structures.

In chapter 2 we review the literature of neuroimaging studies in pediatric OCD and investigate the evidence for a neurodevelopmental basis of pediatric OCD. We were interested to understand the mechanisms behind obsessive and compulsive symptoms and how the brain mediates these symptoms during development. Differences with findings in
adult onset OCD were explored and we focused on developmental findings in pediatric samples.

**Chapter 3** describes our findings of the structural anatomical scans. This study investigates regional brain volume abnormalities in medication-free pediatric OCD patients compared to controls with a whole-brain approach using DARTEL VBM. In addition, we aimed to investigate effects of CBT and associations between therapy effect and regional brain volumes.

We hypothesized, based on the reviewed studies of chapter 2, that pediatric OCD patients have structural abnormalities in gray matter of frontal-striatal circuitry, i.e. the striatum, orbito frontal cortex, lateral and medial prefrontal cortex, anterior cingulate cortex, and in addition the parietal cortex, and white matter abnormalities in the corpus callosum, cingulum, capsula interna/externa and frontal lobe. In addition, we expected gray matter volumes in (para) limbic structures would correlate with symptom severity, and we aimed to investigate whether these abnormalities would normalize after CBT.

**Chapter 4** describes our study of white matter integrity with the diffusion tensor imaging (DTI) technique. DTI is based on the self-diffusion properties of water. The most important measure is fractional anisotropy (FA). FA is a measure of the fraction of the diffusion tensors that contribute to anisotropic diffusion. If the diffusion tensors are equal in all directions, then FA is zero, whereas if the diffusion is preferentially only in one direction, then FA equals 1. FA can be seen as a measure for white matter integrity and connectivity. We hypothesized that pediatric OCD patients compared to controls would show a higher fractional anisotropy in the fronto-striatal-thalamic network and that these difference would change with symptom improvement.

In **chapter 5** we employed a planning paradigm during functional MRI to investigate brain activation patterns in pediatric OCD patients before and after CBT. We used the tower of London task. A task which has showed specific brain activations of the DLPFC and parietal cortex in adult OCD patients.

Task related changes in blood oxygen dependent signal (BOLD) were measured during planning contrasted with a control task (counting) and with increasing difficulty of the planning task (task load).

We hypothesized that paediatric OCD patients compared to healthy controls would perform worse during the task (increased error rates and/or reaction times), associated with reduced recruitment of dorsal prefrontal-striatal areas. Also, we aimed to investigate whether such abnormalities would normalize after successful treatment.
Chapter 6 addresses differences and changes in brain activation patterns during error and high conflict trials in pediatric OCD patients compared to healthy controls before and after CBT. We employed an interference task, the arrow version of the flanker task, to probe the ACC functioning which has been found to be involved in error and high conflict monitoring. We focused in this study on developmental aspects, e.g. age effects, on brain activation patterns. Task related changes in BOLD signal were measured during error trials compared with correct trials and during congruent trials compared with incongruent trials (high conflict) in patients compared to controls before and after CBT. In addition we investigated the effect of age on these BOLD activation patterns. We hypothesized that in paediatric OCD patients the ACC, insular cortex and medial prefrontal areas would be hyperactive compared to controls during error trials and high conflict trials. Furthermore, it was hypothesized that this hyperactivity is a trait feature of OCD, and therefore will not change with symptomatic improvement through CBT. In addition, we aimed to investigate developmental aspects of ACC function in patients relative to controls.

In Chapter 7 we investigated brain activation patterns during selective attention in pediatric OCD patients before and after CBT. We used a dot probe task with emotion eliciting pictures with positive, neutral, threatening and obsessive compulsive relevant content and two stimulus exposure durations in order to be able to distinguish early cognitive control processes from late cognitive control processes and also to allow comparison with several other dot-probe investigations. We hypothesized that children with OCD show a higher selection bias for OCD relevant and threat pictures compared to healthy controls, OCD patients compared to controls show more activation of the amygdala, ACC, PFC or parietal areas and that CBT will normalize selective attention bias and brain activation patterns. In addition, we aimed to explore whether these outcomes were associated with age.

Chapter 8 is an integrative chapter in which we summarize our findings, integrate the different findings in a model, and discuss the implications of our findings, the limitations of these studies and directions for future research.