Neuroimaging studies in pediatric obsessive compulsive disorder
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Chapter 8

Summary and discussion

Neuroimaging studies in pediatric obsessive compulsive disorder
Summary

The aim of this thesis is to investigate differences in brain anatomy and brain functioning of children and adolescents with an obsessive compulsive disorder compared to healthy age companions. In addition we were interested whether the found differences would change after successful cognitive behavioral psychotherapy and whether age would influence brain functioning in children and adolescents with an obsessive compulsive disorder.

In chapter 2 we reviewed neuroimaging studies of pediatric obsessive compulsive disorder (OCD) published until October 2008. We found twenty eight studies regarding a total of 462 patients. These studies varied widely in the techniques used, inclusion and exclusion criteria, design and objectives. Nevertheless we were able to conclude that the aggregated findings indicate a dysfunction of the frontal-striatal circuit. In contrast to adult studies, which report mainly involvement of the caudate nucleus and orbitofrontal cortex, the pediatric studies pointed at an involvement of other basal ganglia structures (putamen, globus pallidus) and the thalamus instead. Outside the frontal-striatal circuit there were findings of differences in (para) limbic circuitry (amygdala, hippocampus and insular cortex), fronto-temporal-parietal and fronto-cerebellar circuits, as well as the corpus callosum and the pituitary gland. We also found indications for an aberrant brain development in pediatric OCD patients. A developmentally mediated network dysplasia was hypothesized, resulting from a different pattern of pruning and myelinisation among several fronto-striatal networks. In OCD, ventral frontal brain regions appear to increase with age, where the opposite is to be expected, whereas dorsal regions decrease more than expected; in contrast, the thalamus and the corpus callosum apparently lack the normal pruning pattern associated with an age-related volume decrease. Treatment studies employing antidepressant drugs (SSRI’s) have reported normalization of structural, functional and neurochemical abnormalities in pediatric OCD, especially in the basal ganglia, thalamus, and amygdala. The two treatment studies employing cognitive behaviourial therapy revealed no changes after therapy.

In chapter 3 we performed a voxel based morphometry (VBM) study in 29 pediatric OCD patients before and after 16 sessions of protocolized cognitive behvioural therapy (CBT). In this study we investigated regional differences in gray (GM) and white matter (WM) volumes between OCD and controls and changes in these volumes after CBT. We found that patients showed larger GM volumes in the anterior pole, insula and parietal cortex and larger WM volume in the cingulum and splenium of the corpus callosum. After CBT these differences remained. However we also found an increase of GM volume of the orbitofrontal cortex and WM volume of the capsula externa over time in OCD patients.
relative to controls. GM volume in orbitofrontal cortex after therapy was correlated with change in symptom severity. This demonstrated that CBT results in an adaptation of the brain to the endophenic abnormalities of pediatric OCD patients. We hypothesised that this adaptation is in the ventral fronto-striatal circuit due to an altered, delayed development of the more dorsal prefrontal regions in pediatric OCD patients.

In chapter 4 diffusion tensor imaging (DTI) was used to investigate differences and changes in white matter integrity. We found higher fractional anisotropy (FA) as a measure of white matter integrity in the corpus callosum of pediatric OCD patients. Treatment effect was seen with a relative increase in FA compared to controls in the corpus callosum and capsula interna. We hypothesize that the modulatory effect of CBT in pediatric OCD patients gives rise to normalization in myelination of the ventral PFC-striatal connections in the genu of the corpus callosum.

In chapter 5 we described a functional MRI study using a planning paradigm, the Tower of London, before and after CBT in pediatric OCD patients. We demonstrated that patients perform the task significantly slower but with similar accuracy compared to controls. Neuroimaging results showed less recruitment of frontal and parietal regions in OCD patients compared to controls during planning versus control task. With increasing task load patients compared to controls showed more recruitment of ventrolateral and medial PFC, as well as insula and anterior cingulate cortex. After treatment, these differences ceased to be significant, time x group x task load interaction analyses showing a significant decrease in right posterior prefrontal activity in OCD patients relative to healthy controls. Changes in symptom severity were correlated with changes in BOLD activation patterns before and after treatment in dorsolateral prefrontal cortex (DLPFC) and parietal cortex. Pediatric OCD patients showed subtle planning impairments and decreased DLPFC and parietal recruitment, which normalized following CBT. With increasing task load patients additionally showed increased activation of medial prefrontal, cingular and insular cortex which normalised as well after CBT. Planning dysfunction is likely to be a state rather than a trait feature of pediatric OCD.

In chapter 6 functional MRI results during error monitoring and high conflict with a Flanker task were described. In this chapter we demonstrated age dependent effects of BOLD activation patterns. During error trials compared to correct trials pediatric OCD patients and controls showed an interaction effect of age x group x time in the rostral ACC and dorsomedial prefrontal cortex. This effect was driven by an increased BOLD activation in older OCD subjects, which was more robust after treatment. During high conflict trials compared with low conflict trials an interaction effect for group x time x age was found in
bilateral insula. This effect was driven by an increase of BOLD in older OCD before but not after treatment. A group x time interaction effect in dorsomedial prefrontal cortex, premotor region and ACC was found. This effect was driven by an increase of BOLD in these areas in OCD subject relative to controls over time. We concluded that children and adolescents with OCD did show an age dependent increase of BOLD signal in the rostral part of the ACC during error responses and in bilateral insular cortex during high conflict tasks, which is only partially affected by CBT. Therefore, rostral anterior cingulate cortex functioning may be a vulnerability factor in OCD, whereas insular functioning may be state dependent.

In chapter 7 we reported on selective attention in pediatric OCD patients using a dot probe paradigm during fMRI before and after CBT. Patients compared to healthy controls showed a negative selective attentional bias (SAB) for OCD relevant and threat pictures, but not for positive pictures. The negative SAB normalized after treatment. Negative emotional pictures gave more activation of the hippocampus in pediatric OCD patients compared to controls before treatment, after treatment hippocampal activation was no longer significant different. Selective attentional processes with OCD relevant pictures showed less activation in DLPFC and parietal areas, threat relevant pictures additionally showed less activation in medial prefrontal, cingular and paralimbic areas like insula and parahippocampal regions in OCD subjects compared to controls. After treatment dorsolateral prefrontal, parietal and insular areas showed an interaction effect for group versus time with an increase of activation in these regions in OCD patients relative to controls. Age was correlated in OCD patients with more recruitment of frontal-striatal-thalamic and insular regions were as controls showed an association with recruitment of the mid frontal region only. We concluded that pediatric OCD patients show SAB for negative emotional pictures with a decreased fronto-striatal and limbic circuits activity which normalizes following CBT. Selective attentional bias is likely to be a state rather than a trait feature of pediatric OCD.
Discussion

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 on a neurobiological level during cognitive behavioral therapy?
3. What are developmental aspects of brain functioning in pediatric OCD patients?

Differences in brain functioning in pediatric OCD:

The main findings in our studies show differences between patients and controls in brain anatomy and brain functioning in the fronto striatal circuit (Table 1). However we also found differences outside the fronto striatal circuit, e.g. the insula and parietal areas. These findings add to the reported findings in chapter 2 of previous neuroimaging studies (Figure 1).

In chapter 2 we described various explanatory models of fronto striatal dysfunction in OCD, e.g. a dysfunctional error detection system (10), basal ganglia dysfunction (88) and a dysbalance in direct and indirect systems of the basal ganglia (170). We concluded, based on the reviewed studies in chapter 2, that dysfunctions might be present at various levels (frontal and striatal/basal ganglia) and indicate involvement of both ventral and dorsal systems.

The present studies show, somewhat surprising, more prefrontal than basal ganglia involvement. The functional imaging studies show hypoactivity of the dorsal lateral prefrontal cortex (DLPFC) and hyperactivity of ventral and medial prefrontal systems in OCD patients compared to healthy controls. The parietal cortex findings are linked with the findings in the DLPFC, whereas the insular findings follow medial PFC activation patterns. This suggest connectivity between DLPFC and parietal cortex and between insular cortex and medial PFC which has been reported in several connectivity studies (81;113;322).

To understand what is happening in the brain in pediatric OCD we have to take into account these findings of dorsal hypoactivity and ventral hyperactivity. The DLPFC is involved in executive functioning, such as planning, working memory and set-shifting, and the parietal cortex is involved in spatio-temporal tasks (203). A dysfunction of these systems could result in uncertainty how to continue, an inability to shift sets, and perseveration of behaviour. The ventral and medial parts of the PFC have been shown to be hyperactive. The mPFC and ACC are involved in error monitoring and solving conflicting stimuli(329), whereas the orbitofrontal cortex is involved in the evaluation of the motivational
significance of stimuli, in generating adaptive responses to rewarding and aversive stimuli and in registering and regulating emotional states (57). Hyperactivity of this system could lead to a heightened state of alertness, in which state every stimulus is important and has to be reacted upon. Especially aversive stimuli trigger this system, as seen during the dot-probe fMRI task. But a deficient dorsal system prevents an adequate response.

Figure 1.

Main findings neuroimaging studies in pediatric OCD of this thesis superimposed on findings of review previous studies (chapter 2). Findings of this thesis are in bold black, grey for changes after CBT. Each symbol is one study (+: Increase of volume or activity, =: no change, -: decrease of volume or activity). Abbreviations: S= Structural imaging; F= Functional imaging. C= Chemistry (Magnetic Resonance Spectroscopy). ACC: Anterior Cingulate Cortex; OFC: Orbito Frontal Cortex; DLPFC: Dorso Lateral Prefrontal Cortex; NC: Nucleus Caudate; GP: Globus Pallidum; rCBF= regional Cerebral Blood Flow (from SPECT study); Glx=Glutamate; N-AA= N-Acetyl-aspartate; Cr =Creatine; Cho= Choline.
Table 1. Brain areas which show differences in brain anatomy or brain functioning before treatment in pediatric OCD patients compared to age and gender matched controls.

<table>
<thead>
<tr>
<th>Main Area</th>
<th>VBM</th>
<th>DTI</th>
<th>fMRI TOL (Task vs. baseline)</th>
<th>fMRI TOL (Increased task load)</th>
<th>fMRI DOT (OCD pictures)</th>
<th>fMRI Flanker (High conflict)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal lateral PFC</td>
<td>Larger GM in anterior pole left</td>
<td>Lower BOLD in DLPFC left</td>
<td>Lower BOLD in DLPFC right</td>
<td>Lower BOLD in DLPFC left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial PFC</td>
<td></td>
<td>Higher BOLD left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral PFC</td>
<td></td>
<td>Higher BOLD left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td></td>
<td>Higher BOLD bilateral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striatum</td>
<td></td>
<td></td>
<td></td>
<td>Lower BOLD Putamen right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>Larger GM left</td>
<td>Higher BOLD left</td>
<td>Lower BOLD right</td>
<td>Lower BOLD right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal Cortex</td>
<td>Larger GM left</td>
<td>Lower BOLD right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WM</td>
<td>Larger WM Corpus callosum and Cingulum</td>
<td>Higher FA in corpus callosum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PFC prefrontal cortex, VBM voxel based morphometry, DTI diffusion tensor imaging, BOLD blood oxygen level-dependent signal, WM white matter, FA fractional anisotropy.

We suggest that the OCD symptomatology is the reflection of this imbalance of ventral and lateral fronto-striatal circuits. This result in an overload of the striatum which has the effect of cognitions becoming conscious which are normally filtered by the striatum, these cognitions form a kind of loop in the prefrontal circuits and are recognised as obsessions. In addition the stereotypical reaction patterns of the striatum are no longer inhibited, resulting in compulsive behaviour (Figure 2). The hyperactivity of the ventral system, which
is highly connected with the limbic system, results in amygdala and insular activation and anxiety. This model, although over simplistic, is able to account for the several aspects of the OCD symptomatology, obsessions, compulsions and anxiety.

In our studies we did find basal ganglia or striatal differences between OCD patients and controls only in one fMRI paradigm (dot probe) which was surprising in the light of the above mentioned hypothesis and earlier work, which indicated involvement of several basal ganglia in pediatric OCD (78;80;229;230;284;285). However several more recent studies did not show evidence of striatal abnormalities in pediatric OCD (37;136;137). This could result from differences in samples, methodology or techniques involved. Also the choice of paradigm influences striatal involvement. To give an example, we did not use a reversal learning task, which is known for its activation of the striatum (223). However it could be
that in pediatric OCD striatal involvement is less prominent compared to adult OCD. This is somewhat counter intuitive since the striatum develops earlier than the prefrontal cortex, so we would expect more similarities in this area with adult populated studies. Our findings could point at the fact that prefrontal abnormalities precede the striatal abnormalities and that only later on in development striatal abnormalities become prominent.

The relationship between our VBM findings and the functional data are somewhat puzzling:

What is the meaning of enlarged volumes in respect to function? If a regional volume is enlarged the function could be compromised and the enlargement reflects a compensatory mechanism of this area to overcome the dysfunction. However it could also be the other way around: enlargement is a sign of better functioning. We found enlargements in the anterior pole, insula and parietal cortex. The larger GM volume of the anterior pole in OCD patients is not reflected in the functional MRI data. This could be due to the fact that the used paradigms are not probing these areas. In general the anterior pole is not often mentioned in fMRI studies because of the susceptibility for artifacts in this region. We think that the increased volume of the anterior pole could reflect the earlier maturation of this area compared with the DLPFC (285) and could be an adaptation to hypoactivation of DLPFC we found in pediatric OCD in the TOL study (Chapter 5).

The increased GM of the insula, although only one sided, corresponded with differences in BOLD signal in this area, higher for TOL increased task load and lower during the dot-probe. This also applies for the parietal volume difference, which was reflected in lower BOLD signal during TOL and dot-probe. In general a lower BOLD signal correlates with a higher regional GM volume; however the insular findings are equivocal. To make it even more complex, an increased BOLD signal does not always coincide with better functioning at the behavioral level. We found no behavioral differences between patients and controls during the flanker task but found differences in BOLD signal.

Discrepancies of this kind we found as well with white matter volumes and fractional anisotropy (FA). We found enlarged WM volumes in the corpus callosum and the cingulum but with DTI we found higher FA only in the corpus callosum.

These discrepancies show the complex relationship between brain and behavior and relevance of the use of well established paradigms to investigate brain functioning in pathologic populations.
The mechanism of change on a neurobiological level during cognitive behavioral therapy.

We explored a repeated measures design with scans before and after therapy, or the same time interval between scans for controls. This design gives the possibility to explore treatment effect through the interaction effect between groups and time (Table 2) and show which circuits are relevant to master the OCD symptomatology. Theories about cognitive control over emotions emphasize a dorsal-ventral discrepancy in which ventral systems generate emotions and appraise valence, whereas tasks that require cognitive control – the ability to volitionally order and allocate resources to meet task demands and satisfy personal goals – utilize more dorsal regions (289). Cognitive behavioral therapy, in this view, could reach effect by enhancing cognitive control over emotions involving reasoning and deliberate, conscious re-framing of schemata, and therefore rely mainly on dorsal circuits, or by making use of the evaluation of context-appropriate emotional values and the selection of actions based on these evaluations, which would involve ventral systems (198).

At least two different patterns of brain volume and activity changes are conceivable: Psychotherapy might lead to a normalization of previously abnormal activation, or it may lead to the recruitment of additional areas and thus attenuate symptoms (147). Our finding of the increase of orbital frontal cortex GM volume in OCD patients over time relative to controls and striatal WM volume increase points at a change in the ventral frontostriatal circuit which seems to be an adaptation to differences between patients and controls, in GM anterior pole and insula volume and WM cingulum and corpus callosum volumes, which were stable over time. So the second hypothesis of recruitment of additional areas to attenuate symptoms seems to apply here.

The increase of medial orbital frontal activity has been described with other neuroimaging CBT treatment studies. In a study of spider phobia, for example, an increase in orbitofrontal activity was seen (255;256). Rolls (227) puts forward that the OFC is crucial for reversal learning, especially emotion-related learning. Damage to the orbitofrontal cortex can impair the learning and reversal of stimulus-reinforcement associations, and thus the correction of behavioral responses when there are no longer appropriate because previous reinforcement contingencies change. Visual discrimination experiments in animals and humans have demonstrated that not only the acquisition of stimulus-reinforcement associations, but also their flexible adjustment, involves the OFC (126). From a learning perspective, CBT can be considered reversal learning.
In chapter 3 we speculate about the meaning of this change in the ventral but not in the dorsal circuit. The dorsal circuit is recruited when more cognitive strategies are used to control emotions (198). We hypothesize that the ventral circuit, which maturates earlier, compensates for the immaturity of the dorsal circuit, a mechanism which has been demonstrated in younger and more anxious children (200).

We found functional but not anatomical changes in the dorsal lateral circuit after CBT, especially an increase in activation patterns during flanker and dot-probe tasks. In addition medial PFC, ACC and insular BOLD signal were also increased after CBT (table 2). In general we could see a normalization of BOLD signals after treatment. Some of these changes were correlated with changes in symptom severity scores, e.g. flanker task changes in BOLD activation in DLPFC and DMPFC, which show that the change in BOLD signal reflects improvement in symptomatology indeed.

We demonstrate that CBT has a modulatory effect on brain anatomy and brain functioning. Our studies show the plasticity of the brain in pediatric populations. Functional changes can occur in dorsal and ventral system but anatomical changes occur in ventral systems only. We are not yet able to discern whether these changes are temporary or permanent. This will be investigated in a follow up study. We wonder also whether these changes are specific for this age group and reflect the plasticity of the prefrontal brain in adolescence. Some findings normalized after CBT which suggest that these findings were state related, whereas other findings remained the same after successful CBT which suggest that these findings are trait related and could be part of the endophenotype of pediatric OCD. Another explanation could be that CBT does not change all OCD symptoms and affect not all patients, which is indeed the case, so the remaining differences could be still reflections of the state the OCD patients are in.
Table 2. Interaction effects

<table>
<thead>
<tr>
<th>Main Area</th>
<th>VBM</th>
<th>DTI</th>
<th>fMRI TOL (Increased task load)</th>
<th>fMRI DOT (OCD pictures)</th>
<th>fMRI Flanker (High conflict)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPFC</td>
<td></td>
<td></td>
<td>Posterior PFC decrease</td>
<td>Increase DLPFC right</td>
<td>Increase DLPFC bilateral</td>
</tr>
<tr>
<td>Medial PFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increase mPFC Left</td>
</tr>
<tr>
<td>Ventral PFC</td>
<td></td>
<td></td>
<td>Increase of GM volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td></td>
<td></td>
<td></td>
<td>Increase ACC left</td>
<td></td>
</tr>
<tr>
<td>Striatum</td>
<td></td>
<td></td>
<td>WM increase Cl, Decrease CE/CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td></td>
<td></td>
<td>Increase left</td>
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<tr>
<td>Parietal Cortex</td>
<td></td>
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<td>Increase Precuneus right</td>
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<td></td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td></td>
<td></td>
<td>Increase FA</td>
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</tbody>
</table>

Table 2. Interaction effects of group over time (treatment) in several brain areas across the several scan modalities.

Several questions remain: What changes? And: How does change occur?

The ‘what’ question is not easy to answer: Change in regional volume could be an in- or decrease in neuropil, neuronal size, arborization, or myelination. Change in FA can be due to neuronal remodeling, loss or secondary astrocytosis, loss of specific fiber tracts, changes in fiber composition, or changes in cell permeability. Change in BOLD signal points at (de)activation of certain brain areas but does not tell whether this is an adaptation to a dysfunction or the dysfunction itself. Also it is not clear at which level, e.g. that of the neuron or of the circuit the dysfunction appears.

It is even more difficult to understand how change occurs. When a non-physical intervention can change the brain, we have to consider how this takes place.
Is it a direct effect of the CBT on the brain areas or is it an indirect effect through a third factor, e.g. symptom change, which influences brain activity. Because of the small number of non-responders we were not able to detect differences between responders and non-responders. However, the correlation between change in symptom severity and the brain change in the brain suggests that it is the change in symptoms which has its impact on brain functioning.

**What are developmental aspects of brain functioning in pediatric OCD patients?**

In our review (chapter 2) we found several studies which point at differences in the neurodevelopment of children and adolescents with OCD compared to healthy controls. An age related volume increase of the anterior cingulate cortex (ACC)(232), and a decrease in dorso lateral prefrontal cortex (DLPFC) (77) volume were observed in OCD patients, but not in healthy controls, whereas an age related volume decrease of the thalamus (80), and an increase in corpus callosum volume (234) were observed in healthy controls but not in OCD patients. These findings suggest a developmentally mediated network dysplasia due to different patterns of pruning and myelinisation among several fronto-striatal networks. The frontal regions increase with age where the opposite would be expected and the thalamus lacks the normal pruning pattern of a decreasing volume with age. However, since these results were obtained exclusively in cross-sectional studies, there is clearly a need for empirical confirmation in longitudinal designs.

Our findings with the flanker task (chapter 6) are of interest with regard to age dependent effects. We found rostral ACC and insular activation to be age dependent in OCD patients and not in healthy controls. This suggests that only after maturation of the adolescent brain we find the typically OCD brain activations found in adult OCD studies(60). However this pathological brain functioning was only partially affected by CBT. Again we see an adaptation of the brain to a pathological state to overcome the OCD symptomatology but the primary deficits (endophenotype) still remain. The time frame of our studies was too short to be able to interpret developmental aspects longitudinally. We did not compare a pediatric sample with an adult sample, so we are not able to investigate whether pediatric OCD is a sub sample or a different disorder compared to adult onset OCD.

**Clinical relevance**

The studies presented in this thesis were not designed to yield knowledge directly applicable in clinical practice. However several aspects have clinical relevance: These studies show that pediatric OCD patients have several brain deficits which can be detected with structural and functional MRI. These brain differences point at the role of
neurobiological mechanisms in pediatric OCD. It shows that during childhood and adolescence these neurobiological abnormalities already exist. Clinicians can use this information in the psycho education of patients and their families.

Although the neuroimaging findings are of interest, they cannot be used as an adjunct to diagnosis at an individual level. The differences we were able to identify are differences between groups, with considerable individual variance. Therefore the MRI is not (yet) a diagnostic instrument in OCD, apart from financial and practical constraints.

These studies show that CBT can influence brain anatomy and functioning in a pediatric population. It is not only with physical interventions as medication, deep brain stimulation (DBS) or repeated trans magnetic stimulation (rTMS) brain functioning can change. These studies underscore the effectiveness of CBT and shed light on the mechanisms behind its effectiveness. The message is that exposure and response prevention train the brain in a healthy way. We demonstrate that change is not always to be found in the affected brain areas but sometimes in other brain areas that compensate for the dysfunction of the affected brain areas. This suggests that after a successful therapy the brain is not “healed but adapted”, with the possibility of relapse or a chronic course. Follow up with booster sessions CBT, as soon as OCD symptoms reoccur, could be necessary to keep the brain in healthy shape.

Our findings are also important in the light of development of new treatment strategies. Deep brain stimulation (DBS) for instance, nowadays used as a treatment in refractory OCD adult populations (52;53), can be informed by studies as ours in deciding upon the localisation of stimulation. We should add that in our opinion DBS should not yet be applied in pediatric populations, as we are not able to judge how this might affect the developing brain, especially in children with severe psychopathology. The same can be said about trans magnetic stimulation (TMS)(264), even more because the effect of rTMS has yet not been established in OCD.

We think that knowledge of underlying neurobiological disturbances in OCD improves the understanding of our patients, inspires the development of new treatment strategies and helps patients and their families to understand their situation.

**Limitations**

Several limitations of the studies in this thesis have to be addressed. The population which has been investigated is heterogeneous: Obsessive compulsive disorder itself is a heterogeneous disorder. Several authors point at the fact that four or five symptom dimensions can be distinguished in pediatric and adult population...
alike(169;272;273) a washing/contamination, checking/aggression, symmetry/ordering and a hoarding dimension and these dimensions has been shown to have different neuroimaging results(170;171;300). In our study population we found a large overlap in symptom dimensions of patients which hampered investigating differences between dimensions, apart from the fact that the groups would become too small to have enough power left for statistical analysis.

We had a large age range (8-18 years) which can delude developmental effects and influence outcome. All results were controlled for age effects and most did not change the outcome. We had more girls than boys in our population (2:1). Controls were matched on age and gender.

The design does not include a placebo treatment group, which renders it difficult to conclude whether our results in the CBT study are a true treatment effect, or an effect of differences in maturation between OCD and controls, just to mention another possibility.

The design did also not include another clinical group which precludes conclusions about the specificity of our findings. Several other psychiatric disorders (depression, tic disorders, PTSD, ADHD and schizophrenia) have abnormalities within the fronto striatal and limbic circuit(289). This could point at a general “psychopathology factor”, although the differences that have been identified are in different parts of these circuits, suggesting differences of a more subtle kind, below the level of a circuit. However since a lot of patients have co-morbid disorders, associated with changes in fronto striatal circuit as well, it can be hard to discern the main effect of the disorder and the effect of co-morbidity. Also a third factor, such as personality or temperament, social economic status, or a history of child abuse could contribute to the found differences.

The neuroimaging techniques have their limitations itself: We have to keep in mind that voxels are not neurons and one voxel of 1 -2 mm³ contains on average hundred neurons (29), tracks in DTI are composed of hundreds of axons and a BOLD signal is reflecting the activity of a group of neurons. The spatial resolution of MRI is too low to detect changes at the level of a neuron. Our hypothesis of circuits which are activated in parallel may be over simplistic, since many interactions which take place between neurons also happen between circuits. The dorsal-ventral dichotomy is appealing as a hypothesis but we have to take in account anterior-posterior, lateral-medial and left-right dichotomies. Probably all these poles are not dichotomous at all but have dimensional distributions. No doubt that brain functioning is more complex than described in our models.
Future research

Longitudinal and multimodal studies are needed to understand the development of the brain in pediatric OCD. Until now only short time follow up data, like ours, are available. The inclusion of a group of patients at risk (children of OCD patients) provides the possibility to detect early signs of aberrant brain development. A comparison with adult OCD patients is necessary to understand the differences between early onset OCD and late onset OCD and the effect of the disorder itself on brain functioning.

In order to understand the mechanisms which influence brain development we need to combine genetic and environmental data with the neuroimaging data. The identified brain abnormalities can be seen as endophenotype, but still need to be linked to specific genetic factors.

We also need to compare our data with other (child and adolescents) psychiatric populations in order to establish the specificity of our findings. Combining the different MRI modalities could be a promising strategy. Strategies which investigate connectivity between brain areas with resting state MRI and DTI are promising. The development of fMRI paradigms which are standardized and well established across several patient groups is needed. Standardization opens the route to larger cohorts (at a multi-center base) which are needed to investigate symptom dimensions, age specific developments and treatment effects.

An approach in which medication, CBT and placebo could be compared with neuroimaging would shed some light on the question whether our findings are specific for CBT or are a general treatment effect and even more important, which patient benefits from which intervention.

Further development of therapeutic approaches and innovations are necessary, such as cognitive remediation training or an inference based approach to reduce therapy resistance and a chronic course.
Conclusive remarks:

OCD in children and adolescents is a complex neurodevelopmental disorder at the intersection of several lines: a developmental line in which the disorder can become manifest early in development but also in adulthood; a psychiatric disorder line in which it can show up together with neurotic disorders like anxiety and depression or with neurodevelopmental disorders like tic disorders and autism spectrum disorders; a neuroanatomical line in which cortical, sub cortical, ventral and dorsal disturbances can be found, and finally a treatment line in which CBT, and sometimes medication, can prove to be effective. Neuroimaging of children and adolescents with OCD brings together all these complex interactions and challenges scientists to disentangle the mechanisms which underlie psychopathology and most importantly discover the interventions which can influence this psychopathology.