Neuroimaging studies in pediatric obsessive compulsive disorder
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Chapter 2

Pediatric obsessive-compulsive disorder, a neurodevelopmental disorder?
Evidence from neuroimaging

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Abstract

Objective: To present an overview of neuroimaging data on pediatric obsessive-compulsive disorder (OCD) and discuss implications for further research. Method: Medline, PsycINFO databases and reference lists were searched for relevant articles. All neuroimaging studies up to October 1, 2008 involving children and adolescents with obsessive-compulsive disorder were included.

Results: Twenty-eight neuroimaging studies using various neuroimaging techniques (CT (2), MRI (15), MRS (8), and SPECT (2), fMRI (2) but no PET or DTI), including a total of 462 pediatric patients, were identified. A number of findings indicate a dysfunction of the prefrontal-striatal-thalamic circuit with the involvement of other basal ganglia structures (putamen, globus pallidus) and the thalamus, in contrast to adult studies which report mainly involvement of the caudate nucleus and orbitofrontal cortex. Several findings point at an aberrant development of the brain in pediatric OCD patients when compared with healthy controls.

Conclusion: Neuroimaging studies have contributed to our understanding of the neurobiological basis of pediatric OCD. This review provides an agenda for further theory driven research, in particular aimed at identifying a critical window of abnormal maturation of prefrontal–striatal–thalamic and limbic circuitry in pediatric OCD patients.

Key words: Obsessive-compulsive disorder, neuroimaging, magnetic resonance imaging, childhood, adolescence, development.
Introduction

Obsessive-compulsive disorder (OCD) is characterised by recurrent and persistent thoughts, impulses, or images, which cause marked anxiety or distress, and repetitive behaviours or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly (5). In half of the patients with OCD, the disorder starts in childhood and has serious consequences for the emotional and social development of these children (121).

Pediatric OCD, also called early onset OCD, differs from late onset, adult OCD with regard to gender distribution which is skewed toward males, a higher prevalence of OCD and tic disorders in relatives, higher co morbidity of tic disorders, but lower with regard to depression (70;72;92). Estimates of the prevalence of OCD in childhood and adolescence in the general population vary widely, from 0.06 to 2 percent, which is likely due to differences in diagnostic criteria, including the distinction with normal obsessive and compulsive phenomena of childhood (95;332). Whereas classical symptoms such as contamination fear and checking compulsions do occur in childhood (92), characteristic OCD symptoms in children are compulsive questioning, symmetry obsessions, and repetitive rituals with magical thinking. Children often have obsessions which they do not recognise as excessive or unreasonable (i.e., ego-syntonic), and obsessions are not always associated with increased anxiety (142). Co morbidity is high: 30% tic disorders, 25% depressive disorder, 24% specific developmental disorder, 17% specific phobia, 16 % generalised anxiety disorder. Externalising disorders, like ADHD or oppositional defiant disorder, are less prevalent (10%) (70;72;276).

Treatment options in pediatric OCD are comparable with adult OCD and include cognitive behavioural therapy (CBT) and medication, especially selective serotonin reuptake inhibitors (SSRI’s) and clomipramine. Effect sizes are modest, slightly higher for CBT than for medication (1;73;197).

The aetiology and pathogenesis of OCD is still insufficiently clear. Several neurobiological models have been proposed, implicating various substructures of the frontal-striatal-thalamic-cortical network (10;19;183), including the hypothesis that neurodevelopmental mediated network dysplasia resulting in ventral prefrontal-striatal abnormalities may underlie pediatric OCD (232). Some authors have suggested the involvement of other structures as well, such as the brainstem (278), the amygdala (222;286) or the corpus callosum (234).

Over the last one or two decades, modern imaging techniques have greatly contributed to our understanding of neuropsychiatric disorders such as OCD. Regarding adult OCD, several excellent reviews of the imaging literature have appeared recently (65;170;252). However,
to our knowledge, a comprehensive overview of imaging studies in pediatric OCD is still lacking.

In the present review, neuroimaging is used as a general term for various modalities aimed at non-invasive mapping of human brain structure and/or function, for diagnostic or research purposes. Several neuroimaging techniques need to be distinguished: (1) modalities which may reveal structural abnormalities, like computerized tomography (CT)-scanning, and structural magnetic resonance imaging (MRI), including Diffusion Tensor Imaging (DTI), to visualize cerebral white matter tracts; (2) techniques assessing cerebral blood perfusion or metabolism, i.e. single positron emission computed tomography (SPECT) and positron emission tomography (PET) using flow tracers (HMPAO for SPECT, $^{15}$O-H$_2$O for PET) or labelled glucose ($^{18}$F-FDG-PET), and functional MRI, all reflecting regional brain activity; (3) techniques which can be used to measure regional biochemical parameters, in particular neuroreceptor binding (ligand-PET and SPECT), and magnetic resonance spectroscopy (MRS). $^1$H-MRS can be used for regional measurements of compounds such as N-acetyl aspartate (NAA), choline (Ch), and myoinositol (mI), considered to be markers of neuronal viability, membrane turnover and myelination, and gliosis, respectively. Consequently, MRS is highly suitable for longitudinal studies of neurodevelopmental processes.

Neuroimaging studies of children have specific advantages and drawbacks. Obviously, it is advantageous to be able to study patients early during development, when potentially confounding factors such as treatment response, use of medication or long-term effects of the disorder itself are absent or limited. On the other hand, there is the disadvantage of the restricted use of radiation dependent techniques such as CT, PET and SPECT in children. Because MRI does not involve the use of radioactive material, it is the most widely used technique in children, with functional MRI (fMRI) and MRS as viable alternatives for radiation dependent techniques. Although fMRI is increasingly being used in pediatric populations, there is still a paucity of data compared with adult populations. Moreover, extrapolation of functional MRI results obtained in adults to children is not straightforward, because of differences in neurovascular coupling, characteristics of biological noise, neuroanatomy, and behavioural performance, which are likely to impact the magnitude and time course of the hemodynamic response (123).

In this article we will review the neuroimaging literature on pediatric OCD and investigate the evidence for a neurodevelopmental basis of pediatric OCD. Arguments for a neurodevelopmental basis of pediatric OCD rather than an acquired degenerative process are the frequent onset of the illness in childhood (121), the similarity between OCD and developmentally normal childhood rituals (57), the high incidence in first degree family members of neurodevelopmental disorders such as Tourette syndrome, which are also
known to often co-occur with OCD (199), and the presence of neurological soft signs that correlate with severity of obsessions and nonresponse to treatment (97;98).

Neuroimaging studies of normal development (42;85;164;268) indicate that gray matter volume follows an inverted U-shape course, with large regional variations. In contrast, white matter volume shows a more or less linear increase during development. Striatal structures mature earlier than prefrontal regions, where maturation continues into early adulthood. Changes of gray matter volumes are likely to result from dendritic arborisation, cell death and synaptic pruning, whereas white matter changes are primarily due to increased myelinisation. These processes allow for fine-tuning and strengthening of connections between prefrontal and subcortical regions leading to greater cognitive control (42).

Neuroimaging data of human cortical development suggest that individual sub regions follow temporally distinct maturational trajectories in which higher-order association areas mature only after lower-order sensorimotor regions have matured. Additionally, it appears that phylogenetically older cortical areas mature earlier than the newer cortical regions (85). 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 these maturational patterns may underlie neurodevelopmental pathology.

Method

A systematic review was performed of the literature on neuroimaging in pediatric and/or adolescent OCD. Eligible studies were identified through a search of journal abstracts in the MEDLINE and PsycINFO databases from the last 20 years up to October 1, 2008. Search terms included “obsessive-compulsive disorder,” “imaging”, “magnetic resonance imaging”, “child”, “adolescence”. The search was limited to English-language articles describing studies with human subjects in childhood and adolescence. In addition, citations from all identified articles were individually searched in an iterative fashion for other relevant studies.

Results

Twenty-nine studies (table 1-3) were identified, with a total of 462 pediatric OCD patients (two studies (181;284) included some patients also enrolled in previous studies (265;285;286). These studies employed several neuroimaging techniques (CT (2), MRI (15), MRS (8), fMRI (2) and SPECT (2)). No studies with DTI or PET were found. Most studies (21)
compared OCD patient with healthy controls (HC), two studies performed a within-group comparison without controls, four studies included a second clinical group as well, and one study included a high-risk group (unaffected siblings). Most studies were cross-sectional. Eight studies employed a factorial design with measurements before and after treatment.

**Volumetric CT/MRI studies.**

Two studies using CT scanning and 15 studies using structural MRI were identified. These studies differed in regions investigated, method of analysis (Region of interest method (ROI) or voxel-based morphometry (VBM)), and patient inclusion criteria with regard to comorbidity.

ROI methods, although still considered the gold standard, may differ in neuroanatomical criteria employed to delineate anatomical regions, require extensive training of the raters, are time-consuming and carry the risk of low inter-rater reliability. The newer VBM method is an automated method in which structural images are segmented on a voxel by voxel basis and subsequently warped to an anatomical standard space, so that individual volumetric differences will appear as differences in gray (or white) matter density. Potential confounds in this method are differences in gray/white matter contrast between groups and misclassification of voxels due to partial volume effects, among others (14;174). The methods seem to supplement each other (83).

Most studies in pediatric OCD have targeted the fronto-striatal–thalamic circuit (see figure 1).
### Table 1

**Structural neuroimaging studies (CT and MRI) in pediatric OCD:**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Technique</th>
<th>Participants</th>
<th>Main results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behar et al.</td>
<td>1984</td>
<td>CT scan</td>
<td>17 adolescents OCD vs. 16 controls</td>
<td>Increase of ventricle-cortex ratio in adolescents with OCD predicted by decreased striatal volumes</td>
<td>Ventricle-brain ratio Co-morbid depression</td>
</tr>
<tr>
<td>Luxenberg et al.</td>
<td>1988</td>
<td>CT scan</td>
<td>10 male Childhood onset OCD vs. 10 controls Mean age 20.7</td>
<td>Bilateral decreased volume of nucleus caudate in adolescents and young adults with OCD</td>
<td>Region of interest (ROI) method Limited number of participants Not pediatric OCD, broad age range</td>
</tr>
<tr>
<td>Rosenberg et al.</td>
<td>1997a</td>
<td>MRI</td>
<td>19 pediatric patients with OCD 19 controls Mean age 8 years</td>
<td>Reduction of volumes of putamen but not nucleus caudate or prefrontal volumes. Inverse correlation symptom severity of obsessions (not compulsions) and volume putamen.</td>
<td>ROI method Co-morbidity high, only 7 with only OCD</td>
</tr>
<tr>
<td>Rosenberg et al.</td>
<td>1997b</td>
<td>MRI</td>
<td>21 pediatric OCD 21 controls Mean age 12.7</td>
<td>All corpus callosal regions except the isthmus were significantly larger in OCD than in controls. CC area correlated with OCD symptom severity but not illness duration. The age-related increase in CC size seen in normal subjects was absent in OCD patients.</td>
<td>ROI method Co-morbidity anxiety disorders was high</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Method</td>
<td>Imaging</td>
<td>Subjects</td>
<td>Findings</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>Rosenberg and Keshavan</td>
<td>1998</td>
<td>MRI</td>
<td></td>
<td>21 pediatric OCD patients and 19 controls</td>
<td>Increase of volume of the anterior cingulate no other regions (DLPFC, OFC, posterior cingulate) in pediatric OCD patients. Correlation with obsessional severity not compulsions. In controls reduction of ACC volume by age not in OCD patients.</td>
</tr>
<tr>
<td>Gilbert et al.</td>
<td>2000</td>
<td>MRI</td>
<td></td>
<td>21 pediatric OCD patients and 21 controls</td>
<td>Before treatment increase of volume thalamus (n=21) after paroxetine (up to 60 mg for 12 weeks) normalisation (n=10). No differentiation within thalamus nuclei. Small sample size after medication</td>
</tr>
<tr>
<td>Rosenberg et al.</td>
<td>2000</td>
<td>MRI</td>
<td></td>
<td>11 Pediatric OCD patients</td>
<td>Before treatment increased thalamic volume but no normalisation of increased volume after cognitive behavioural therapy Small sample size Short duration of CBT No healthy controls</td>
</tr>
<tr>
<td>Giedd et al.</td>
<td>2000</td>
<td>MRI</td>
<td></td>
<td>34 patients with PANDAS (18 primary OCD, 16 primary tic disorder) 82 health controls</td>
<td>Increase of volume of nucleus caudate, putamen en globus pallidus but not the thalamus in PANDAS versus healthy controls. No differences between tic or OCD subjects Heterogeneous sample size for OCD. ROI method. Not able to obtain reliable thalamic volumes.</td>
</tr>
<tr>
<td>Peterson et al.</td>
<td>2000</td>
<td>MRI</td>
<td></td>
<td>59 child patients: 15 OCD, 33 Tic</td>
<td>No association was found between OCD patients and basal ganglia enlargement (Nucleus caudate, putamen and globus Heterogeneous sample size for OCD. Adults and children</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Key Findings</td>
</tr>
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</tr>
<tr>
<td>Szeszko et al.</td>
<td>2004</td>
<td>MRI</td>
<td>11 pediatric psychotropic naive patients</td>
<td>11 healthy controls</td>
<td>Asymmetric amygdala volume Le&gt;Ri in OCD but not in HC. Normalisation after paroxetine up to 60 mg for 16 weeks. No correlation between volume changes and symptom changes.</td>
</tr>
<tr>
<td>Szeszko et al.</td>
<td>2004</td>
<td>MRI</td>
<td>23 psychotropic naive pediatric OCD patients</td>
<td>27 HC</td>
<td>Smaller Globus Pallidus but not Nucleus Caudate, Putamen or white matter. Increased volume of total gray matter in anterior cingulate gyrus in OCD.</td>
</tr>
<tr>
<td>Gilbert et al.</td>
<td>2004</td>
<td>MRI</td>
<td>21 pediatric OCD vs. 15 HC</td>
<td></td>
<td>Negative correlation between age and gray matter concentration in DLPFC in controls, not in OCD.</td>
</tr>
<tr>
<td>MacMaster et al.</td>
<td>2006</td>
<td>MRI</td>
<td>31 drug-naïve pediatric OCD patients</td>
<td>31 matched healthy controls</td>
<td>Pituitary volume was significantly smaller (11%) in OCD patients. Increase in volume with increase with age (pt and HC). Inverse correlation between severity of compulsions, not obsessions and decrease of volume.</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Study Type</td>
<td>Sample Size</td>
<td>Age</td>
<td>Findings</td>
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<tr>
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<tr>
<td>2006</td>
<td>Amat et al.</td>
<td>MRI</td>
<td>100 patients, mean age = 11.4 (62 TD, 28 OCD, 45 ADHD)</td>
<td>32 HC, mean age = 10y</td>
<td>Cerebral hyperintensities (CHI) were more seen in patients than HC. TD 28.8%, ADHD 45%, OCD 21.4%. More subcortical CHI than cortical CHI in patients than in HC.</td>
</tr>
<tr>
<td>2007</td>
<td>Gilbert et al.</td>
<td>MRI</td>
<td>10 pediatric psychotropic naive OCD, mean age=13.3</td>
<td>10 unaffected siblings, mean age=13.1</td>
<td>10 HC Mean age=13.0</td>
</tr>
<tr>
<td>2007</td>
<td>Carmona et al.</td>
<td>MRI</td>
<td>18 OCD (10 on medication, 8 medication naive, sex ratio 13 boys, 5 girls)</td>
<td>Mean age 12.9</td>
<td>18 HC mean age 13.0 Matched for age and gender</td>
</tr>
</tbody>
</table>

**Co morbid group**

**VBM**

**First study with unaffected siblings**

**Small sample size**

**Partly medicated patients**
| Szeszko et al. | 2008 | MRI | 37 OCD patients drug naïve mean age 13.0 26 HC matched for age and gender | More gray matter in bilateral putamen en orbital frontal cortex in OCD versus HC. Higher symptom severity correlated with greater left putamen en right OFC gray matter. VBM results were confirmed by manual ROI measurements. In addition greater gray matter in Anterior cingulate cortex was found with ROI. | VBM confirmed with manual ROI measurements. Largest cohort Medication naïve patients |

Abbreviations: ACC= anterior cingulate cortex, ADHD=attention deficit disorder, CBT=cognitive behavioral therapy, CC=Corpus Callosum, CHI=cerebral hyperintensities, CT=computed tomography, CTD=chronique tic disorder, DLPFC=dorso lateral prefrontal cortex, HC=healthy control, MRI=magnetic resonance imaging., OCD=obsessive compulsive disorder, OFC=orbital frontal cortex, ROI=region of interest, SFG=superior frontal gyrus, TD=Tourette disorder, VBM=voxel based morphology.
Figure 1. Main findings pediatric OCD neuroimaging studies in fronto-striatal-thalamic circuit. Each symbol (=,+ or -) is one study with reference number. 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.
Prefrontal regions, together with anterior cingulate cortex, were investigated in six studies (37;77;78;232;284;285).

The anterior cingulate cortex (ACC) showed an increase of volume in pediatric OCD patients versus HC in two independent studies using ROI methods (232;285). In a recently published study (284), no differences in volumes of gray matter in the ACC were found with optimised VBM, whereas a ROI analysis showed an increase of gray matter in this structure. The authors suggest that these contrasting findings are due to the use of anatomically relevant “parcellation units,” based on sulcal anatomy, in ROI, whereas VBM is focused on discrete regions within the anterior cingulate that are maximally different between groups. It is therefore plausible that anterior cingulate abnormalities are more widely distributed throughout the structure. In contrast, two studies (37;78) using whole-brain VBM reported a reduction in gray matter concentration in ACC (bilateral (37) or left-sided only (78). These conflicting findings may be due to a number of factors, including data analysis method (ROI or (optimized) VBM), different selection criteria (co-morbidity, age, gender, severity of illness) and low power. A near-significant positive correlation between regional ACC volume and age has been found in a cross-sectional study (232).

The orbital frontal cortex (OFC) has been investigated in two VBM studies (37;284). Carmona et al. (37) reported reductions in gray matter concentration in bilateral frontal regions in pediatric OCD patients compared to age and sex matched HC. In addition, these authors reported decreased white matter in bilateral frontal and right parietal regions in OCD patients versus HC. In contrast, Szeszko et al. (284) showed an increase of gray matter in orbital frontal cortex which was confirmed by analyses of manually drawn regions of interest.

In the dorsolateral prefrontal cortex a negative correlation between age and gray matter concentration was found in HC, but not in OCD (77). These data suggest neurodevelopmental pathology in ACC and DLPFC in OCD, but since longitudinal data are not available yet, cross-sectional data linking age and volume should be interpreted with caution.

The striatum and basal ganglia have been investigated in 8 studies (37;74;78;149;202;235;284;285). In a CT imaging study (149), bilateral decreased volume of the caudate nucleus was found in adolescents and young adults with OCD. One MRI study (235) reported a decrease of putamen volume but not of the caudate nucleus, whereas another study (285) reported a decrease in volume of the globus pallidus but not of the putamen or caudate nucleus (both with a ROI method).
In a VBM study Gilbert et al (78) compared OCD patients to a high-risk group of unaffected siblings. The OCD patients showed greater gray matter density in the right putamen but not in the left striatum. However, another VBM study (37) did not find basal ganglia differences between OCD and HC. When performing a post-hoc analysis, a significant correlation between age and left caudate GM volume was found in OCD patients but not in HC. In the OCD group, drug treatment duration was positively correlated with GM volumes of the left putamen, right caudate and bilateral thalamus. However, after regressing out age as a potential confound, these effects ceased to be statistically significant. Szczesko et al. (284) found increased gray matter volumes in bilateral putamen (VBM and ROI methods) in pediatric OCD patients compared to HC. These authors did not find differences in gray matter volume of the putamen between OCD patients with contamination/cleaning symptoms compared to patients with aggressive/checking symptoms.

In a special subgroup of OCD, the pediatric autoimmune neuropsychiatric disorders associated with Group A β-hemolytic streptococci (‘PANDAS’), an increase in volume of the caudate nucleus, putamen and globus pallidus has been demonstrated (74). Another study (202) investigated the correlation between streptococcal titres and basal ganglia enlargement. Although no enlargement in the OCD group was found, these authors observed an association between streptococcal titres and basal ganglia enlargement, globus pallidus and putamen, in ADHD and OCD patients. This suggests that not OCD as such, but the occurrence of streptococcal infection is the determining factor in basal ganglia enlargement. But the involvement of neuroimmunological factors in OCD is still a matter of scientific dispute (50;128).

In summary, from the ROI studies it appears that OCD is characterized by a decrease in basal ganglia volume, although the nuclei involved differ between studies. If autoimmune or inflammatory factors are involved, an enlargement of these nuclei is found. However, until now newer VBM studies have not been able to replicate these findings.

The thalamus was investigated in three studies (74;80;230). An increase of thalamic volume has been found in pediatric OCD, when compared to HC (80). This increase normalised after 12 weeks of successful paroxetine treatment (doses up to 60 mg). However, in a pre-post treatment design without HC, 12 weeks of cognitive behavioural therapy (CBT) did not result in a change in thalamic volume (230), although patients showed a significant reduction of symptoms as well. These findings suggest that changes in thalamic volumes, as found in the Gilbert et al. study, are a specific effect of paroxetine treatment rather than clinical remission per se. In the PANDAS subgroup (74) no difference in thalamic volume was observed. Also, VBM studies (37;78;284) did not show thalamic volume differences.
A negative correlation of thalamic volume with age in OCD patients but not in HC was found in a cross-sectional design (80;231). OCD patients had a decrease in volume with increasing age, whereas HC did not show a change of thalamic volume related to age. This pattern therefore differs from the results in ACC and DLPFC reviewed above, which revealed age-related volume changes in HC but not OCD subjects.

Outside the fronto-striatal-thalamic circuit, the **corpus callosum**, the **amygdala**, the **hippocampus** and the **pituitary gland** have been investigated in pediatric OCD in independent single studies, which are therefore in need of replication. The corpus callosum (CC) was found to be significantly larger in pediatric OCD patients than in controls, not including the isthmus (234). CC volume was significantly correlated with OCD symptom severity but not with illness duration. The age-related increase in CC volume observed in normal subjects was absent in OCD patients. The amygdala was found to be asymmetric (l>r) in drug naive pediatric OCD patients but not in HC in a ROI study(286). After paroxetine medication up to 60 mg for 16 weeks this asymmetry disappeared due to reduction of the left amygdala volume. The reduction in left amygdala volume correlated significantly with paroxetine dosages and total cumulative exposure to paroxetine between the scans, but did not correlate with changes in clinical measures.

A VBM study (37) reported a significant negative correlation between symptom severity and bilateral hippocampus gray matter volume.

The volume of the pituitary gland was found to be significantly smaller (11%) in pediatric OCD patients (154). Pituitary volume proved to correlate positively with age (in OCD and HC). A negative correlation was found between pituitary volume and severity of compulsions, but not obsessions.

Cerebral hyperintensities (CHI) have been observed more often in pediatric patients than HC: Tourette Disorder 28.8% (p 0.02), ADHD 45% (p 0.01), OCD 21.4% (p 0.10, not sign.) (4). Subcortical CHI has been observed more frequently than cortical CHI in these patients relative to HC. These findings suggest that, for a substantial subgroup at least, lesions of subcortical regions (traumatic or inflammatory) play an important role in the aetiology of these disorders. However, the absence of a significant correlation of basal ganglia volume with the presence of cerebral hyperintensities in the basal ganglia in this study suggests that if an inflammatory process is responsible for the cerebral hyperintensities, the inflammation is likely to be restricted to the vascular bed after the acute initial parenchyma oedema subsides, as is also the case in Sydenham’s chorea (75). These observations therefore appear to be in agreement with the correlation between streptococcal titres and basal ganglia enlargement reviewed above(202).
**Functional imaging studies:**

Functional studies of pediatric OCD populations with SPECT and PET are rare, due to restrictions in the use of radioactive material in young subjects. Until now, only two SPECT studies have been published (45;54). Recently, two fMRI studies, which do not entail the use of radioactive materials, have become available (137;317).

In SPECT-studies (or PET-studies with 18F-labelled glucose) the subject needs to remain passive during 45-60 minutes while the scan is being made. A drawback of these so-called resting state studies is therefore the limited control over the subjects’ mental activity; in other words, experimental conditions are not easy to constrain. As a result, differences between patients and HC may be difficult to interpret since these may be confounded by e.g. differences in (anticipatory) anxiety between patients and HC. For this reason, researchers have switched to multi-scan techniques (15O-PET, due to the short half-life of 15O, and fMRI), which permit within-session comparisons between two or more conditions, usually ‘task vs. baseline’. In psychiatry research, investigators have used symptom provocation (or symptom capture) designs, alternating ‘symptom’ and ‘baseline’ conditions, and cognitive paradigms with both neutral and emotional stimuli. The latter paradigms are generally based on previous neuropsychological findings of cognitive dysfunctions in psychiatric patients. Therefore, functional imaging during performance of such tasks aims at identifying the neural substrate of specific cognitive abnormalities in various psychiatric disorders.

In a resting state SPECT study, increased regional cerebral blood flow (rCBF) in bilateral dorsolateral prefrontal cortex, anterior cingulate cortex and caudate nucleus was reported in pediatric OCD patients versus HC (54). After 12 weeks of SSRI medication (paroxetine at a fixed dose of 20 mg) these differences disappeared. Between responders and non-responders, no differences in rCBF reductions were found.
Table 2

Functional neuroimaging studies (SPECT and fMRI) in pediatric OCD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Technique</th>
<th>Participants</th>
<th>Main results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diler et al.</td>
<td>2004</td>
<td>SPECT</td>
<td>18 pediatric non-medicated OCD patients (11-15 y) and 12 age matched healthy controls</td>
<td>Increased cerebral blood flow bilateral dorsolateral prefrontal cortex, cingulate and nucleus caudate in OCD patients which normalised after paroxetine 20 mg for 12 weeks. Responders and non-responders did not differ in rCBF. However responders had changes in 3 regions and non-responders in only one after treatment.</td>
<td>Small group Fixed dosage Short treatment duration</td>
</tr>
<tr>
<td>Castillo et al.</td>
<td>2005</td>
<td>SPECT</td>
<td>14 pediatric OCD patients before and 10 patients after treatment with clomipramine (2-13 month) Mean age 13.4</td>
<td>Negative correlation between age of onset and rCBF in areas of frontal lobe and parietal cortex. No differences before and after treatment in rCBF in any region of the brain.</td>
<td>Small sample size Heterogeneous patient group Great differences in treatment length. No healthy control group</td>
</tr>
<tr>
<td>Woolley et al.</td>
<td>2008</td>
<td>fMRI</td>
<td>10 boys with OCD after successful treatment (8 SSRI and 5 CBT) mean age 14.3 9 HC mean age 14.5</td>
<td>During the ‘stop’ task, the boys with OCD showed reduced activation in inferior and orbital fronto-striato-thalamic brain regions. Stop failures were associated with reduced activation in the OCD group in mesial and dorsolateral prefrontal cortex, including the</td>
<td>Small sample size Treated OCD patients, low symptom level Mixed medication and CBT</td>
</tr>
</tbody>
</table>
control tasks

anterior cingulate gyrus. During the more cognitive inhibition tasks the OCD group showed reduced activation in inferior frontal (switch task) and temporo-parieto-cerebellar regions (motor Stroop and switch tasks).

| Lazaro et al. 2008 | fMRI with a serial reaction task with simple and complex sequences | 12 OCD (drug-naïve, 5 girls, 7 boys) mean age 13.7 before and after treatment with SSRI. 12 age, gender, IQ matched HC | OCD patients had increased activity in bilateral middle frontal gyrus compared to controls during the performance of a complex motor task before treatment. After treatment, patients shower higher activation in a region of the right inferior parietal lobe. CY-BOCS total score was positively correlated with the left nucleus accumbens and with a region in the superior right parietal lobe. The CY-BOCS obsessions subscale was positively correlated with a region in the superior right parietal lobe and a region in the left cingulate gyrus. The comparison between baseline state and post pharmacological treatment in OCD patients showed significant decreased activation in left insula and left putamen. |

Small sample size
Homogene patient group
Well matched control group

Abbreviations: SPECT=single proton emission computed tomography, rCBF=regional cerebral blood flow, fMRI=functional magnetic resonance imaging.
In contrast, another SPECT treatment study (45) failed to reveal rCBF differences before and after treatment with clomipramine. In this study, a negative correlation between age of onset and rCBF was observed in frontal and parietal cortical areas. These results are difficult to interpret since the study did not include a control group, and included a very heterogeneous sample with regard to co morbidity, medication status and duration of treatment.

The first fMRI study in pediatric OCD (317) studied 10 boys with OCD after treatment and 9 HC. Event-related fMRI was used to compare brain activation patterns during three different tasks of inhibitory control, i.e. a stop task (measuring the ability to suppress an already triggered motor response), a motor Stroop task (involving a stimulus-response spatial incompatibility effect), and a switch task (requiring cognitive switching between two spatial dimensions). No significant behavioural differences were found between OCD patients and HC in any of the tasks. The fMRI data revealed that in pediatric OCD subjects compared to HC frontostriatal regions were hypoactive during the stop task, whereas the Stroop and switch task data revealed not only (inferior) frontal but also temporo-parietal and cerebellar regions of hypoactivity. These latter findings are somewhat unexpected, suggesting involvement of structures associated with attention rather than inhibitory control. Furthermore, it is interesting to note that task-specific abnormalities in pediatric OCD are not limited to frontostriatal structures but extend to fronto temporo-parietal and fronto-cerebellar circuits.

A second fMRI study (137) included 12 OCD patients before and after SSRI treatment (fluoxetine 20-60 mg) and behavioural counselling, with a control group of 12 subjects.

A blocked fMRI design was used employing a serial reaction task with two alternating conditions of simple and complex sequences. Before treatment, OCD patients showed higher activity in bilateral middle frontal gyrus compared to controls. Correlation analysis of clinical measurement (CY-BOCS data) and brain activation showed a positive correlation of activation of the left nucleus accumbens (with CY-BOCS total), superior right parietal lobe (with CY-BOCS total and CY-BOCS obsessions) and left cingulate gyrus (with CY-BOCS obsessions only). After treatment, OCD patients showed more activation in the right inferior parietal lobe than controls. Comparisons between baseline and post-treatment scans (pharmacological and behavioural therapy) showed reduced activation in left insula and left putamen.

In summary, the latter study showed higher levels of frontal activation but not striatal activation in OCD patients before treatment during an implicit learning task, whereas in the Woolley et al. study reduced activations were observed, predominantly during inhibitory
tasks. Apart from differences in fMRI paradigms, this discrepancy may have been due to differences in clinical characteristics, in particular symptom severity.

**Brain chemistry**

Brain chemistry has been investigated in eight studies with MR proton spectroscopy (¹H-MRS) in which a number of brain regions were examined (21;58;181;229;236;237;245;265), treatment protocols have been evaluated (21;236) and comparisons were made with another clinical group (depressed children) (181;237;265). ¹H MRS enables direct and non-invasive measurements of brain chemistry in vivo. Compounds that can be measured are N-acetyl-aspartate (NAA), glutamergic compounds (Glx), choline (Cho), creatine (CR) and myoInositol (ml). NAA is a marker for neuronal viability and its concentration declines in neural tissue before neuronal loss can be detected by means of structural MRI. Decreased NAA levels are associated with impaired neuronal function (58). Glx is a measure for glutamergic excitatory neurotransmission (237). Cho concentrations reflect levels of choline-containing compounds, such as phosphocholine, glycerophosphocholine and acetycholine. Decreased Cho concentrations have been observed in regions of acute demyelination in multiple sclerosis patients, and are believed to reflect myelin abnormalities (265). Altered brain creatine-phosphocreatine levels might reflect changes in brain energy use (181). A limitation of ¹H MRS use is that due to its low signal to noise ratio data acquisition is limited to a single voxel or small volume in the brain. In the anterior cingulate cortex (ACC), glutamate concentrations were found to be reduced in both OCD and major depression but not in HC (237). Concentrations of other chemical compounds like NAA, choline or creatine were similar across groups. In a second study, an increase of NAA was found in the left dorsolateral prefrontal cortex (245). Concentrations of other chemical compounds (Cho, Cr, Glx, and ml) did not differ between patients and HC. Two treatment studies have focused on striatal metabolism in a pre-post design. In the first (236), an increased glutamate concentration in the caudate nucleus was observed before treatment in pediatric OCD compared to HC, which normalised after 12 weeks of paroxetine medication up to 60 mg/day. This reduction of Glx concentration was correlated with treatment response (C-YBOCS scores). Of the other components, creatine tended to be increased as well, whereas N-AA, Cho and ml showed no differences. In another treatment study, no change was found in any of the neurochemical compounds in the left caudate nucleus after CBT treatment (21). This latter study did not include HC.
Table 3 Spectroscopic neuroimaging studies with proton magnetic resonance ('H MRS) in pediatric OCD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Technique</th>
<th>Participants</th>
<th>Main results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzgerald et al.</td>
<td>2000</td>
<td>'H MRS</td>
<td>11 pediatric OCD 11 healthy controls Mean age 11.19</td>
<td>Decrease of concentration N-acetyl-aspartate (ratio with choline) in medial thalamus but not lateral thalamus. These abnormalities are more on the right than left side. Correlation with obsessions not compulsions.</td>
<td>Small sample size No comparison with other brain regions</td>
</tr>
<tr>
<td>Rosenberg et al.</td>
<td>2000</td>
<td>'H MRS</td>
<td>11 pediatric OCD 11 healthy controls Mean age 11.0</td>
<td>Increase of glutamate concentration in nucleus caudate before treatment which normalise after paroxetine medication (flexible dosage up to 60 mg for 12 weeks). Increase of creatine in NC near significance before treatment.</td>
<td>Small sample size Comparison with occipital region. Short treatment duration No placebo control</td>
</tr>
<tr>
<td>Rosenberg et al.</td>
<td>2001</td>
<td>'H MRS</td>
<td>11 pediatric OCD 11 healthy controls</td>
<td>Only cystolic choline is increased but not N-acetyl-aspartate or creatine in bilateral medial thalamus. Not in lateral thalamus.</td>
<td>Small sample size Multiple measurements in thalamus. No comparison in other brain regions</td>
</tr>
<tr>
<td>Russell et al.</td>
<td>2003</td>
<td>'H MRS</td>
<td>15 pediatric OCD (5-15 year) 15 HC Mean age: 12.01</td>
<td>Increase of N-AA in the left but not right DLPFC. No differences in choline and creatine concentrations in DLPFC.</td>
<td>Only 2 voxel measurements. Small sample size</td>
</tr>
<tr>
<td>Benazon et al.</td>
<td>2003</td>
<td>'H MRS</td>
<td>21 treatment naive pediatric</td>
<td>No effect of CBT on change in concentration of neurochemical markers in left caudate head</td>
<td>Single voxel measurement</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Method</td>
<td>Group Information</td>
<td>Findings</td>
<td>Additional Information</td>
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<tr>
<td>Rosenberg et al.</td>
<td>2004</td>
<td>¹H MRS</td>
<td>20 pediatric OCD (M.A. = 11.4), 14 depression (M.A. = 15.6), 14 HC (M.A. = 15.5)</td>
<td>ACC Glutamate concentrations were reduced in both OCD and MDD group vs. healthy controls. No differences in NAA, choline or creatine concentrations.</td>
<td>Single voxel measurement</td>
</tr>
<tr>
<td>Mirza et al.</td>
<td>2006</td>
<td>¹H MRS</td>
<td>27 treatment naïve pediatric OCD (M.A. = 10.3), 18 pediatric major depression (M.A. = 14.3), 18 HC (M.A. = 14.4)</td>
<td>Increased left and right medial thalamic creatine-phosphocreatine concentrations in patients with obsessive-compulsive disorder compared with both healthy controls and patients with major depression.</td>
<td>Two voxel measurement. Only creatine data. Cross-sectional. Same patient group as Smith 2003</td>
</tr>
</tbody>
</table>

Abbreviations: ¹H MRS = proton magnetic resonance spectroscopy, N-AA = N-acetyl-aspartate
The thalamus has been studied most frequently using MRS. In one study (58), a decreased NAA/choline ratio in medial but not lateral thalamus was found. These abnormalities were predominantly right-sided. In contrast, another study (229) found that only choline was increased (not NAA or creatine) in the bilateral medial thalamus. In a study with three groups (265) comparing pediatric OCD patients with depressed pediatric patients and HC, an increase of choline in bilateral medial thalamus was found in patients with OCD but not in depressed patients or HC. Further analyses revealed increased bilateral medial thalamic creatine-phosphocreatine concentrations in patients with OCD as well, but not in depressed patients or HC (181). From these studies it might be concluded that the medial nucleus, but not the lateral nucleus of the thalamus is involved in OCD but not in major depression. This suggests that this finding is specific for pediatric OCD.

In summary, these spectroscopic studies have shown various abnormalities in different brain regions, i.e. DLPFC: N-NA (245); ACC: glutamate (237); striatum (caudate nucleus): glutamate (236); thalamus (medial nucleus): N-NA (58), choline (229;265) and creatine (181).

Discussion

The ascent of neuroimaging studies over the last two decades has contributed considerably to our understanding of the neurodevelopmental basis of pediatric OCD. Whereas most studies support the hypothesis of dysfunctional prefrontal-striatal-thalamic circuitry, there is also evidence for involvement of (para) limbic circuitry (amygdala, hippocampus and insular cortex), fronto-temporo-parietal and fronto-cerebellar circuits, as well as the corpus callosum and the pituitary gland. Furthermore, although some findings in pediatric OCD converge with those in adult OCD (65;170;224), there are also important differences. The involvement of the OFC and caudate nucleus that emerged from a meta-analysis of functional neuroimaging data of adult OCD patients (315), has only been replicated in one pediatric study for the OFC (284). Pediatric OCD neuroimaging data point at the involvement of other basal ganglia structures (putamen, globus pallidus) and thalamus instead. This may be due to a lack of investigations targeting the former areas but may also reflect a different neuropathological substrate of pediatric OCD compared with late onset adult OCD. A greater involvement of the putamen/globus pallidus and thalamus in pediatric OCD versus prefrontal cortex/caudate nucleus in adult OCD might also explain differences in co morbidity: Tourette syndrome and pervasive developmental disorder, which co-occur more often with pediatric OCD, have been linked to basal ganglia dysfunction, whereas depression, a more prominent co morbid condition in adult OCD, has been associated with prefrontal dysfunction (28). This is not only interesting from a neuropathological but also
from an evolutionary perspective, given that brain areas involved in disorders associated with pediatric OCD are phylogenetically older than the areas involved in co morbid disorders of adult OCD. These subcortical structures mature earlier during normal neurodevelopment than the frontal regions, which continue to mature into late adolescence (164).

Cross-sectional studies in pediatric OCD patients suggest abnormalities of brain development, demonstrating an age-related volume increase of the ACC, as well as a decrease in DLPFC volume in OCD patients but not in HC (77;232). Also, an age-related volume decrease of the thalamus, and an increase in corpus callosum volume was observed in HC but not in OCD patients (80;235). These findings suggest a developmentally mediated network dysplasia due to different patterns of pruning and myelinisation among several fronto-striatal networks. In OCD, ventral frontal brain regions appear to increase with age, whereas the opposite would 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. However, since these results were obtained exclusively in cross-sectional studies, there is clearly a need for empirical confirmation in longitudinal designs.

The findings of MRS studies, especially of N-AAA and choline abnormalities (245;265), in the DLPFC and the thalamus may similarly reflect different patterns of apoptosis, pruning and myelinisation in these areas in pediatric OCD patients, given that N-AAA abnormalities have been associated with neuronal loss and those of choline-containing compounds with demyelination.

Is pediatric OCD a precursor of adult OCD, or a pathogenetically distinct subtype? Only a few studies could be identified in which early onset OCD patients were compared directly with late onset patients (34;105;210;277). Bussato et al. (34), using SPECT, showed that early-onset OCD subjects had decreased rCBF in the right thalamus, left anterior cingulate cortex, and bilateral inferior prefrontal cortex relative to late-onset subjects. Two other studies in which serotenergic function in early versus late onset OCD was investigated with the aid of radioligand SPECT (210) and PET (105) reported that midbrain-pons serotonin binding was higher in early-onset versus late onset OCD. Findings from these studies support the hypothesis that early-onset OCD is a subtype rather than a precursor of late onset OCD, in view of the fact that abnormalities found in OCD subjects were not associated with illness duration. However, it should be noted that “early onset” OCD is often a retrospective diagnosis in which the onset of symptoms rather than the diagnosis per se is taken as the date of illness onset. So “early onset” or “childhood onset” is not necessarily.
equivalent to “pediatric”, as operationalized in this review of pediatric OCD. Furthermore, because long-term follow-up data are not yet available, pediatric neuroimaging data do not allow inferences with regard to adult outcome.

Within those pediatric studies which accounted for age of onset or duration of illness (37;74;152;153;232;234;235;284), no correlations were found with volume change, biochemical parameters as measured using MRS, or activation patterns. Lower age of onset (but not duration of illness) was associated with higher activity of frontal and parietal cortices in one SPECT study (45).

Involvement of the thalamus may be a disorder-specific feature of pediatric OCD given that thalamic biochemical abnormalities were found in OCD but not in depression (181;237;265). These findings also suggest that choline and creatine abnormalities may be useful neurobiological markers for pediatric OCD, but it should be kept in mind that studies directly comparing pediatric OCD to other neurodevelopmental disorders such as ADHD and Tourette syndrome have not yet been published.

In view of these specific findings for OCD vs. depression, it is somewhat surprising that none of the reviewed studies showed significant correlations between neuroimaging data and depression or anxiety symptom severity in OCD (21;37;54;80;137;152;232;284-286). The majority of pediatric OCD patients studied were treatment naïve, thereby ruling out effects of medication on brain volume, function and chemistry as an explanation. 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 (54;80;137;236;286). Two studies employing CBT (21;230) failed to produce similar results for the thalamus (230) and caudate nucleus (21) in recovered patients. This suggests that basal ganglia and thalamic changes are due to SSRI treatment, rather than to symptomatic improvement. In adult OCD, differential patterns of glucose metabolism (using FDG-PET) have been found to predict response to medication or CBT: higher pre-treatment metabolic activity in the OFC was associated with a favourable response to CBT but not fluoxetine treatment. In contrast, lower metabolic activity in the OFC predicted a favourable outcome of fluoxetine treatment (32). However, OFC involvement has not been investigated in pediatric OCD CBT studies.

The mechanism(s) of medication-induced brain volume changes, especially due to SSRI’s, is not yet clear. SSRI’s may lower neural activity, as was shown in a SPECT study of Diler et al. (54), which could arguably result in hypotrophy of neural tissue. Possibly, down regulation of serotenergic receptors following SSRI administration may lead to a reduction in volume, whereas volume changes may also be secondary hemodynamic effects of SSRI’s.
How do these findings relate to the symptomatology of OCD? The orbitofrontal cortex is involved in the evaluation of the motivational significance of stimuli, in generating adaptive responses to rewarding and aversive stimuli, in switching behaviour, and in registering and regulating emotional states. If this region is overactive, normal evaluation of the consequences of immediate action may be disrupted, resulting in uncontrolled thoughts and behaviours (10;57). The (dorsal) anterior cingulate cortex is associated with error-detection and self-monitoring, and its dysfunction is assumed to lead to repetitive actions and increased anxiety (10;38;40). The dorsolateral prefrontal cortex is involved in so-called executive functions, such as planning, working memory and set-shifting; its dysfunction may lead to uncertainty in action planning and perseveration of behaviours, among others (99;203). The limbic part of the striatum (ventral striatum) is likely to be involved in reward-driven learning processes, whereas the dorsal striatum appears to be involved in the procedural learning of behavioural routines that are performed almost without conscious effort (88). Experimental evidence suggests that the striatum is involved in the type of procedural or implicit learning that results in automated responses, roughly equivalent to habits. This type of learning differs from hippocampus-based learning, which builds memories that are dependent on particular environmental cues (87). The thalamus consists of several nuclei of which the medial-dorsal and the ventro-lateral nuclei send vast projections towards the ACC and the OFC. The thalamus regulates cortical activity through differential laminar connections, providing not only feedback, but also initiating “feed forward” loops, via nonreciprocal projections, that influence higher cortical areas. Consequently, the thalamus serves as a relay for basal ganglia output within specific cortical circuits and mediates the information flow between cortical circuits (172).

Five cortico-striatal-thalamic loops have been described (3;28) (see also figure 1), including a motor circuit (involving the supplementary motor areas and the putamen), an oculomotor circuit (frontal eye fields and caudate), a DLPFC circuit (DLPFC and caudate), a lateral orbitofrontal cortical circuit (LOFC and caudate) and an ACC circuit (ACC and ventral striatum). In OCD, the lateral OFC circuit, the ACC circuit and the DLPFC circuit have received most attention from researchers.

Some authors assume dysfunctional error detection to be the central problem in OCD, implying ACC and OFC dysfunction (10). Deficient error detection, which is also a feature of frontal lobe syndromes, reduces the subject’s ability to perceive the reinforcing nature of environmental changes. If this occurs, responses to this type of information will become repetitive and less efficient, leading to behavioural perseverance (257). Alternatively, obsessions and compulsions may be viewed as a result of a hyperactive error detection system, which is activated repeatedly and inappropriately in response to various situations.
The clinical manifestation of this hyperactivity might be the sense that “something is wrong”, a basic impression reported by OCD patients (10). This would result in the emergence of intrusive and pathological thoughts leading to recurrent compulsive behaviours.

Others consider basal ganglia dysfunction (88) to be the core issue in OCD: primary striatal dysfunction in OCD is believed to lead to deficits in thalamic filtering, which in turn leads to exaggerated OFC activity. Striatal dysfunction is hypothesized to underlie implicit information processing deficits, whereas hyperactivity in OFC and other limbic–paralimbic regions is believed to mediate the obsessions and anxiety symptoms of OCD. Information which is normally processed automatically through the striatum may intrude into the conscious domain (the prefrontal cortex), resulting in obsessions, and behavioural selection may become narrowed to compulsive acts (88;222).

A refinement of this neuroanatomical model of OCD (170;222;252) proposes the involvement of direct as well as indirect cortico-striato-thalamic pathways. In the direct pathway, an excitatory glutaminergic signal projects to the striatum, sending an inhibitory gamma-aminobutyric acid (GABA)-ergic signal to the internal part of the globus pallidus. This signal results in a decreased inhibition (disinhibition) of the thalamus and thus an increased excitatory effect on the prefrontal cortex. In the indirect pathway, the striatum projects an inhibitory signal to the external part of the globus pallidus and the subthalamic nucleus, sending an excitatory signal to the internal part of the globus pallidus. The net effect is an increased inhibition of the thalamus and decreased excitation of the prefrontal cortex. It is hypothesized that the direct pathway functions as a self-reinforcing positive feedback loop and contributes to the initiation and continuation of behaviours, whereas the indirect pathway provides a mechanism of negative feedback which is important for the inhibition of behaviours, and for switching between behaviours. The direct pathway is associated (through dopamine D1 receptors) with a ventromedial frontal-striatal circuit including the ventral ACC, orbitofrontal cortex, and ventral striatum linked to the amygdala. The indirect pathway is associated (through dopamine D2 receptors) with a dorsolateral prefrontal-striatal circuit including the dorsal prefrontal cortex, dorsal ACC, and dorsal striatum. An imbalance between these frontal-striatal circuits might mediate OCD symptomatology (65;205;206;224). Based on the positive effects of selective serotenergic re-uptake inhibitors on OCD symptoms and the modulatory effects of serotonin on dopaminergic transmission, it has been suggested that failure of the serotenergic system results in decreased inhibition of the dopaminergic activity within frontal-striatal circuitry. However, interactions between these two systems are as yet insufficiently understood; similarly, little is known with regard to (abnormal) lateralization within each system.
The neuroimaging studies in pediatric OCD reviewed in the present paper suggest that dysfunctions may be present at various levels (frontal and striatal/basal ganglia) and indicate involvement of both ventral and dorsal systems. However, volumetric studies and MRS studies point at the involvement of predominantly subcortical structures (globus pallidus and medial nucleus of the thalamus) in pediatric OCD compared with studies in adults. Also, the repeatedly identified volumetric changes in the putamen suggest additional involvement of motor circuits as well, which may be due to less advanced functional segregation in pediatric populations associated with immature myelinisation.

These findings of “deeper” (i.e., subcortical) structural changes in pediatric population during early development suggest that these changes are primary, and that findings in adult populations should be considered secondary, as a result of, or adaptation to, these primary deficits. Alternatively, it is conceivable that pathology “migrates” during the course of the disorder. Finally, the possibility that patterns of co morbidity (tic disorder, pervasive developmental disorders, depression) contribute to differences between adult and pediatric neuroimaging data in OCD cannot be ruled out.

Taken together, the hypothesis of a developmentally mediated network dysplasia due to differential patterns of pruning and myelinisation within fronto-striatal networks in pediatric OCD (232) still stands, although the dysplasia of the ventromedial OFC and the striatum as postulated by Rosenberg & Keshavan (232) is likely to extend to other parts of cortico-striatal-thalamic circuitry, especially cortical areas such as DLPFC and ACC, and other subcortical regions including the thalamus. Thus, we are led to conclude that in pediatric OCD dysfunction of several cortical-subcortical circuits, in particular at the level of the thalamus and basal ganglia, results in aberrant information and emotion processing. In addition, data indicating temporo-parietal involvement, as discussed in this review, imply that the hypothesis of dysfunctional frontostriatal-thalamic networks in OCD needs to be expanded to account for the role of (para) limbic structures and the cerebellum.

The present review also has limitations that need to be addressed. Comparisons between the reviewed studies need to be made with caution for a number of reasons. First, patient groups were generally small (10-37 patients, mean 20), heterogeneous with regard to age, gender, duration of illness, medication use, severity of symptoms, and symptom dimensions, and were generally characterized by high co morbidity. Two studies were only available in abstract (77;233). Treatment studies differed with regard to length of therapy (2-13 months) and choice of medication. Second, in these studies various imaging modalities have been employed, with hardware (scanners) from various manufacturers; moreover, experimental design and data-analytical strategies differed among studies as
well. For example, whereas most VBM (voxel based morphometry) studies used modulated scans, in others the older method of unmodulated warping was employed, which is likely to be less sensitive to GM/WM volume differences. Therefore, the available studies do not allow a quantitative meta-analysis. In addition, the specificity of many findings is unclear, since few studies have included clinical comparison groups, and abnormalities in fronto-striatal-thalamic circuitry have been reported in several other disorders such as ADHD, autism and tic disorders (28). Volumetric differences between pediatric OCD patients and HC, which have been demonstrated in several cortical and subcortical areas, are often inconsistent. Some studies have observed enlargement of brain areas while others have found diminished volumes of these same areas. As discussed previously, these differences are likely to be explained by several factors, including sampling differences and power issues, but also heterogeneity with regard to aetiological factors. For example, autoimmune reactions (especially following streptococcal infections) were found to be associated with enlarged basal ganglia volume and may explain, rather than diagnosis per se, volume differences (4;74;202). Data analysis methods appear to be another source of heterogeneity: While studies employing a ROI (region of interest) approach (232;235;285) have shown enlargement of prefrontal cortical areas coupled with volume decrease in the basal ganglia, two studies using VBM (37;78) have reported reductions of gray matter concentrations in the prefrontal cortex but no change, or even an increase, in the basal ganglia. In addition, the only study which combined both techniques, in the largest sample until now (284), showed an increase of gray matter volume in prefrontal cortex as well as in the basal ganglia. As was discussed previously, these differences between ROI- and VBM-based methods may be explained by the fact that region-of-interest approaches reflect volumetric differences across an entire brain structure whereas VBM is sensitive to small-scale volumetric differences within such regions.

A final issue that needs to be addressed, when comparing pediatric and adult onset OCD, is the heterogeneous nature of OCD. A four-factor model has shown to provide the best fit in adult as well as in child and adolescent samples. Its four dimensions are: (1) sexual/aggressive/religious/somatic/checking; (2) symmetry/ordering/repeating/counting; (3) contamination/cleaning; and (4) hoarding obsessions/compulsions (168;170;171;272;273). There is some evidence that the neural substrate of these dimensions is different, at least in adult OCD (171;221;300), which may explain a number of inconsistent imaging findings in adult OCD, and possibly also in pediatric OCD. Again, the – admittedly sparse - evidence is mixed, because a recent study (79) failed to observe structural differences between symptom dimensions in adult OCD, and the first VBM study in pediatric OCD addressing this issue also yielded negative findings (284). However, these
null results do not rule out the possibility of different functional abnormalities between symptom dimensions in pediatric OCD patients.

These limitations reflect the state of the field, which is still in a descriptive, explorative phase and lacks clear theoretical models. Furthermore, it is not yet clear how neuroimaging data are related to neuropathology; for example, what causes volume differences and how reduction of increased regional brain volumes following treatment does occur: are pruning processes involved, are volume changes due to neural cell proliferation or cell loss, or are other structures (e.g., glial changes) involved as well? Also, although neurovascular coupling mechanisms are reasonably well understood, at least for the visual cortex (18), the significance of increased or decreased BOLD-responses with regard to regional brain function and connectivity is much less clear.

However, these limitations should not detract from the main findings of this review. The present comprehensive overview of the quickly expanding literature on neuroimaging studies of pediatric OCD demonstrates that the field is not in need of exploratory studies of yet other neuroanatomical areas of interest. Such a strategy would only contribute to the impression of rather mixed, often inconsistent findings that emerges from this review. Instead, new studies should preferably be theory driven, and this review allows the identification of promising lines of investigation. First, abnormal associations between age and regional brain volume in various prefrontal and subcortical areas, together with biochemical abnormalities as identified using MRS, point at a developmentally mediated network dysplasia in pediatric OCD. Pruning of neural networks and myelinisation is a feature of normal development, but is likely to follow different pathways in pediatric OCD. If there are critical windows of abnormal maturation of prefrontal–striatal–thalamic and limbic circuitry in pediatric OCD patients, this might explain, at least in part, why studies of adult OCD patients failed to detect comparable abnormalities. To further investigate this issue, longitudinal studies are needed to monitor developmental abnormalities together with the emergence of obsessive and compulsive behaviour. Second, the field has a clear need for additional functional imaging studies employing activation paradigms aimed at identifying the neural substrate of cognitive abnormalities in pediatric OCD; in addition, these studies should include clinical control groups such as ADHD and tic disorder. Next to fMRI and volumetric MRI, DTI may prove to be valuable in assessing white matter integrity. An integrated approach with multimodal imaging techniques employed in the same subjects, with multiple tasks, each probing a different level of the circuits identified in this review, in a longitudinal design with an adequate sample size, careful matching of patients and controls (e.g. age, gender, handedness, intelligence), in homogeneous patient groups (with regard to co morbidity,
medication, severity of symptoms, symptom dimensions, age of onset) is likely to be the most promising strategy. This should allow researchers to chart neurodevelopmental abnormalities over time, both at a neuroanatomical and a functional level, and to investigate whether pediatric OCD is a distinct subgroup, or dimension, of OCD, or a precursor of adult onset OCD. OCD in children and adults is a severely impairing and relatively treatment resistant disorder. A better understanding of the underlying developmental neurobiological processes is conditional for the much needed improvement of its treatment.