Neuroimaging studies in pediatric obsessive compulsive disorder
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Chapter 6:


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Abstract

Background: Heightened error and conflict monitoring are considered central mechanisms in obsessive compulsive disorder (OCD) and are associated with anterior cingulate cortex (ACC) function. Pediatric obsessive compulsive patients provide an opportunity to investigate the development of this area and its associations with psychopathology.

Methods: Repeated measures were carried out using functional MRI during the performance of an interference task; the arrow version of the Flanker paradigm, before and after cognitive behavioral treatment of twenty-five medication free pediatric obsessive-compulsive patients compared with age and gender matched healthy controls.

Results: During error trials compared to correct trials pediatric OCD patients and controls showed an interaction effect of group x time x age in the ACC and insula. This effect was mainly driven by an increased activation in older OCD subjects which was also present after treatment. During high conflict trials compared with low conflict trials a group x time x age interaction effect was found in bilateral insula. This effect was driven by an increase of BOLD in older OCD patients before but not after treatment. In addition, 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 OCD subjects relative to controls over time.

Conclusions: Compared to healthy controls, children and adolescents with OCD show increased activation of the ACC during error responses and in bilateral insular cortex during high conflict tasks, which is age dependent and which is only partially affected by cognitive behavioral therapy. Therefore, we suggest that anterior cingulate cortex functioning is a vulnerability marker in pediatric OCD, whereas insular dysfunction may be state dependent.

Key words: Obsessive compulsive disorder, fMRI, error monitoring, cognitive behavioral therapy, Child
Introduction

Heightened error detection has been proposed as a central mechanism in obsessive compulsive disorder (OCD) (10). In this view, obsessions are considered the permanent error awareness in various situations, resulting in heightened emotional tension with a preoccupation with correcting perceived mistakes. High conflict stimuli and error awareness could lead to indecision and the feeling of being “stuck”. Compulsions occur as behavioral responses aiming to relieve the tension generated by these situations. Error detection and conflict monitoring have been associated with the anterior cingulate cortex (ACC), insular cortex, and medial prefrontal areas (10;26;39;243).

The investigation of error detection and conflict monitoring with fMRI in adult OCD patients has shown a main effect of task in medial prefrontal/dorsal anterior cingulate and insular cortex, as well as increased ACC activity in patients relative to controls (59;159;296;328). In these studies, a variety of interference paradigms, presenting high conflict situations and aimed at eliciting error responses, has been used: a modified continuous-performance task (297), a Go/No Go task (160), a Multi-Source Interference Task (330), and a Flanker task (61). It is noteworthy that none of these fMRI studies employed a repeated measures design, so that it could not be established whether any abnormalities were state- or trait-related. Furthermore, until now, such studies have only been performed in adult OCD patients, so little is known about the developmental aspects of error detection and conflict monitoring in OCD.

The present study extends this previous work by investigating pediatric OCD patients before and after cognitive behavioral therapy (CBT). Error detection and conflict monitoring were investigated with an interference paradigm, the arrow Flanker task, which has been used before in fMRI studies on OCD (55;60), and has the advantage of being independent of the reading ability of children.

We hypothesized that in pediatric OCD patients the ACC, insular cortex and medial prefrontal areas would be hyperactive compared to controls during error trials and high conflict trials. Furthermore, it was hypothesized that this hyperactivity is a trait feature of OCD, and therefore will not change with symptomatic improvement through CBT. In addition, we aimed to investigate developmental aspects of ACC function in patients relative to controls.
Method

Subjects

Twenty-five OCD patients performed the Flanker task while functional MRI data were collected. Inclusion criteria were age between 8 and 19 years, diagnosis of obsessive-compulsive disorder with a CY-BOCS score of at least 16, and OCD symptoms present for at least six months. Exclusion criteria were IQ below 80, use of psychotropic medication, recent state of the art cognitive behavioral treatment, and presence or history of major psychiatric illness, or metal in or at the body.

Patients were recruited from the outpatient department of our specialized center for children and adolescents with OCD. Twenty-five healthy controls pair-wise matched for age and gender were also recruited.

The present study is part of a larger study which investigates (neuro) psychological and biological mechanisms of change during cognitive behavioral treatment in pediatric OCD.

We have published recently from this larger study on data of a fMRI study during a planning task (Tower of London) (103).

Following baseline measurements (T0), all patients were treated with 16 sessions of manualised CBT (93;316), consisting of exposure with response prevention and cognitive therapy suited to the needs of the patients. Treatment was performed by trained cognitive behavioral psychotherapists (no investigators) and supervised by the author of the manual (EdH).

After 16 sessions of CBT (T1), 24 patients were rescanned (one patient stopped treatment). 22 controls were rescanned after the same period of time (one control refused rescanning, data from two scan sessions had to be discarded due to technical problems).

The study was approved by the Ethical Committee of the Academic Medical Center in Amsterdam (MEC 06/053#06.17.0749). All patients and controls and their parents gave written informed consent.
Measurements

Diagnostic screening was performed by senior clinicians using a semi-structured interview (Anxiety and Depression Inventory Schedule, Child and Parents’ version (ADIS C/P)) (261). The presence and severity of OCD symptoms were assessed with the Child version of the Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (254) by one of the investigators (LHW). All subjects were screened with the Childhood Depression Inventory (CDI) (124) for depression and the State-Trait Anxiety Inventory for children (STAI-C) (269) for anxiety. The child behavior checklist (CBCL) (2) was administered to assess overall functioning and the OC-scale (196) was administered to rule out the presence of OCD symptoms in controls. During scanning subjects were asked to rate their state anxiety level on a 1-10 scale. Intelligence was assessed with the WISC-IV (312) (age <17) or WAIS (311) (age >17) with two subtests, i.e. block design and vocabulary. At rescanning (T1), we obtained STAI-C, CDI and anxiety ratings during scanning for all subjects and CY-BOCS scores for patients only.

Task

Subjects performed an arrow version of a Flanker interference task (56) which required them to focus on a central arrow to make a response according to the direction of the central arrow while ignoring peripheral arrows. The task contained two conditions, i.e. congruent flankers (>>>>> or <<<<< ) and incongruent flankers (<<<<< or >>>>>). The task started with a central cross on a grey background (1000 ms), after which the flanker arrows were projected for 200 ms, followed by a blank grey response slide with a maximum response time of 600 ms. A jittered inter-trial interval of 0, 250, 500, 750 or 1000ms preceded the next trial (84) (Figure 1).

Subjects first practiced outside the scanner to ensure familiarity with the task. Inside the scanner they performed another 10 trials before starting the actual task of 240 trials which lasted on average 11 minutes. The whole scanning procedure consisted of a T1-weighted structural scan, two other fMRI paradigms, the Flanker task and a DTI scan, so that the actual time in the scanner for each subject was one hour.
Figure 1. Flanker task. Trial starts with a fixation point for 1000 ms, then the flanker slide is shown with a congruent flanker <<<<< or >>>>> or an incongruent flanker <<<>< or >><> for 200 ms after which a blank response slide is shown for 600 ms. The inter trial time varies with 0, 250, 500, 750 or 1000 ms (jitter) with a blank slide. Participants have to indicate the direction of the center arrow.

Data acquisition

Imaging was performed on a 3.0T Intera MR system (Philips Medical Systems, Best, the Netherlands) with a 6-channel SENSE head coil. Head immobilization was established using foam pads inside the coil. Stimuli were generated by a personal computer with E-prime software (Psychology Software Tools, Sharpsburg, USA) and projected on a screen at the end of the scanner table at which the subject could look through a mirror above the coil. Two response boxes were used to record each subject’s responses. Anatomical imaging included a coronal gradient-echo T1-weighted sequence (flip angle 8°, repetition time (TR) 9.69 ms; echo time TE=4.60 ms, 182 slices, 256 x 256 pixels, voxel size 1x1x1.2mm, Field of View 218mm x 256mm x 256mm). For fMRI an echo planar imaging sequence (TR 2.3 sec, TE 30 ms , 96 x 96 pixels, FOV 220mm x 120mm x 220mm) was used, creating whole brain acquisitions (40 axial slices, 2.29mm x 2.29mm in plane resolution, 3.0 mm slice thickness). In total, 250 echo planar imaging volumes per subject were scanned.
**Data analysis**

Demographic and behavioral data were analyzed with SPSS software (version 17.0; SPSS Inc, Chicago, Ill). A two-sample t-test was used for investigating differences between patients and controls, repeated measures ANOVA for investigating differences before and after treatment between groups.

Imaging data were analyzed using SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK) running in Matlab version 7.4.0(Mathworks, Sherborn, MA). Preprocessing consisted of correcting the time series for slice acquisition times and image realignment. Next, the EPI volumes were normalized to a standard MNI (Montreal Neurological Institute) template. We used the adult-derived template of SPM5 because there is evidence that for functional analyses in this age range, differences when comparing adult and child brains are negligible (112). Finally, data were smoothed using an 8mm Gaussian kernel.

Data were analyzed voxel-wise in the context of the General Linear Model (GLM) to calculate statistical parametric maps of t-statistics for condition-specific effects. For each subject parameter estimates were calculated for four regressors: Correct Congruent trials, Correct Incongruent trials, Incorrect Congruent trials, and Incorrect Incongruent trials. Contrast images were computed for errors versus correct answers (incongruent and congruent trials were pooled across conditions to obtain sufficient power), and incongruent versus congruent flankers (only correct trials) for each subject. These contrast images were entered into second level (random effects) analyses using ANCOVA with time as a within-subject and group as a between-subject variable and age as a covariate to identify effects of treatment and age. Subsequently, we performed repeated measures ANOVA with time as a within-subject and group as a between-subject variable, as well as two sample t-tests comparing patients at T0 versus controls at T0 and patients at T1 versus controls at T1, and with age as a regressor to calculate interaction effects of group x age, and finally with age as a single regressor in each group.

Post hoc correlations of symptom severity (CY-BOCS score) and BOLD activation patterns at T0 and T1 in patients, and correlations between changes in symptom severity and changes in BOLD activation were calculated in a multiple regression model. Results are reported at a p<0.05 corrected for multiple comparisons using the False Discovery Rate method with minimum cluster extent of 5 voxels.

In addition, effects within our regions of interest, i.e. dorsomedial prefrontal cortex, anterior cingulate cortex, and insular cortex, were assessed at p<0.001 uncorrected (Z>3.09) , using additional small volume correction in SPM5 with a 16mm diameter sphere.
around the peak voxel to correct for multiple testing. These areas were determined on basis of the MNI coordinates corresponding with these regions in the AAL (Automated Anatomical Labeling) template provided in MRIcron

(http://www.cabiatl.com/mricro/mricron/).

**Results**

*Demographic and clinical data (table 1)*

OCD patients had high rates of co-morbid disorders, i.e. 48% anxiety disorders, 12% affective disorders, 12% externalizing disorders (ADHD and ODD) and 8% tic disorder. None of the subjects were using psychotropic medication, one OCD patients had previously used fluoxetine (stopped since 6 months); one patient used risperidone (stopped 14 days before scanning) and one had used methylphenidate, dexamphetamine and atomoxetine (stopped 1 year before scanning). The groups did not differ with respect to age, sex ratio and handedness. Intelligence scores on vocabulary and block design were significantly higher for controls but were all within the normal range. Patients scored significantly higher than controls on the OCS scale of the CBCL, the STAI and the CDI, although only two patients were in the clinical range of depression. State anxiety scores in the scanner did not differ significantly between patients and controls.

Following treatment with 16 sessions CBT, CY-BOCS scores decreased significantly (mean, 24.9 to 13.04 (SD 9.62)). Response (reduction >30 %) was established in 19/24 patients and 16/24 patients reached a CYBOCS below 16.

**Table 1**. Demographic and clinical data of patients and controls.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Patients N=25</th>
<th>Controls N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean 13.95 SD 2.52</td>
<td>Mean 13.71 SD 2.85</td>
</tr>
<tr>
<td></td>
<td>Range 9.0-19.0</td>
<td>Range 8.7-18.8</td>
</tr>
<tr>
<td>Gender</td>
<td>16 girls-9 boys</td>
<td>16 girls-9 boys</td>
</tr>
<tr>
<td>Handedness</td>
<td>22 right, 3 left</td>
<td>23 right, 2 left</td>
</tr>
<tr>
<td>Intelligence</td>
<td>Block design= 9.4 SD 3.1</td>
<td>Block design= 11.2 SD 2.7 §</td>
</tr>
<tr>
<td></td>
<td>Vocabulary= 10.5 SD 1.9</td>
<td>Vocabulary= 12.0 SD 1.49 ‡</td>
</tr>
<tr>
<td>CBCL</td>
<td>Internalizing 20.8 SD 8.1</td>
<td>Internalizing 2.7 SD 3.8 †</td>
</tr>
<tr>
<td></td>
<td>Externalizing 13.8 SD 7.8</td>
<td>Externalizing 2.3 SD 2.8 †</td>
</tr>
<tr>
<td></td>
<td>Total score 61.0 SD 20.7</td>
<td>Total score 9.2 SD 8.7 †</td>
</tr>
<tr>
<td></td>
<td>OCS scale 9.7 SD 3.0</td>
<td>OCS scale 0.67 SD 1.3 †</td>
</tr>
<tr>
<td>Depression (CDI)</td>
<td>T0 11.6 SD 6.2 (2 cases &gt;19)</td>
<td>4.3 SD 3.5 †</td>
</tr>
</tbody>
</table>
### Behavioral data

On the flanker task accuracy rates were lower and reaction times were longer between conditions (incongruent versus congruent; table 2), but did not differ between subjects.

Following treatment, accuracy increased and reaction times decreased but group by time effects were not significant. Age was correlated with accuracy (Congruent trials $r=.662$, $p=0.001$, and Incongruent trials $r=.591$, $p=0.002$) but not with mean reaction time. CY-BOCS scores of patients were positively correlated with accuracy scores on incongruent trials ($r=.413$, $p=0.046$) but not on congruent trials or with mean reaction time. In a split analysis patients with high CY-BOCS scores (>24) were more accurate on incongruent trials than those with a low score ($t=2.561$ (df 23), $p=0.017$). CY-BOCS score were not correlated with age. No significant correlations were found for intelligence scores, depression or anxiety scores, and performance on the flanker task.
Table 2.

<table>
<thead>
<tr>
<th></th>
<th>OCD T0</th>
<th>OCD T1</th>
<th>HC T0</th>
<th>HC T1</th>
<th>Significance between groups</th>
<th>Significance within subjects over time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reaction Time in ms of Congruent Flanker trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td>461</td>
<td>447.8</td>
<td>475</td>
<td>467</td>
<td>NS</td>
<td>F=9.91, df1, p=0.003</td>
</tr>
<tr>
<td>in ms</td>
<td>SD 42.8</td>
<td>SD 52.3</td>
<td>SD 51.9</td>
<td>SD 51.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reaction Time in ms of Incongruent Flanker trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td>519</td>
<td>497.2</td>
<td>531</td>
<td>517</td>
<td>NS</td>
<td>F=16.963, df1, p&lt;0.000</td>
</tr>
<tr>
<td>in ms</td>
<td>SD 47.1</td>
<td>SD 50.2</td>
<td>SD 52.7</td>
<td>SD 51.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accuracy on Congruent Flanker trials (N=120)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy on</td>
<td>110.8</td>
<td>113.5</td>
<td>111.9</td>
<td>115.1</td>
<td>NS</td>
<td>F=9.411, df1, p=0.004</td>
</tr>
<tr>
<td>Congruent trials</td>
<td>SD 6.67</td>
<td>SD 8.3</td>
<td>SD 8.2</td>
<td>SD 8.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(92.4%)</td>
<td>(94.5%)</td>
<td>(92.7%)</td>
<td>(95.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accuracy on Incongruent Flanker trials (N=120)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy on</td>
<td>94.6</td>
<td>100.4</td>
<td>92.5</td>
<td>101.4</td>
<td>NS</td>
<td>F=16.928, df1, p&lt;0.000</td>
</tr>
<tr>
<td>Incongruent trials</td>
<td>SD 14.1</td>
<td>SD 11.6</td>
<td>SD 18.3</td>
<td>SD 8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(79%)</td>
<td>(83.6%)</td>
<td>(77.1%)</td>
<td>(84.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Behavioral data.
Reaction time in ms and accuracy on the Flanker task at baseline (T0) and after cognitive behavioral therapy (patients only) or the same amount of time (controls)(T1).

**Imaging data**

**Error trials versus correct trials (table 3)**

Interaction analysis of group x time x age effects during error trials compared to correct trials revealed effects in the ACC and insula. A group x age interaction analysis showed an increased response in older OCD patients relative to control subjects in rostral ACC at both time points. A time x age effect was found in the ACC, indicating an increased response in older subjects at T1 for both groups. A change over time in BOLD in the right insula was found in both groups as well. Group x age analysis at T0 revealed an effect of age in OCD patients relative to controls in ACC, whereas group x age at T1 again showed an effect for ACC and insula in OCD relative to HC. Within group, OCD patients showed an effect of time x age in ACC and insula (increase over time associated with age), whereas HC did not show any interaction over time with age. Subsequent analyses revealed in the OCD group a positive correlation between age and activation during error responses at T0 in the rostral
ACC (Figure 2A-B). Following treatment (T1), the correlation in the rostral ACC was still present. These correlations were absent in controls at both time points. Also in OCD patients, at baseline (T0) CY-BOCS scores were positively correlated with BOLD signal in right insular cortex. In both groups, error trials compared to correct trials at T0 were associated with greater BOLD signal in the medial prefrontal cortex, bilateral insular cortex, and left parietal cortex. Controls showed in addition activation of the left superior frontal gyrus, and the right parietal cortex and temporal lobe (Table 4 and Figure 3).

**Table 3. Imaging results for error trials versus correct trials**

<table>
<thead>
<tr>
<th>Region</th>
<th>side</th>
<th>MNI</th>
<th>CS</th>
<th>Z</th>
<th>p(FDR)</th>
<th>p(SVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x time x age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>left</td>
<td>-12 21 36</td>
<td>7</td>
<td>3.40</td>
<td>0.912</td>
<td>0.014</td>
</tr>
<tr>
<td>Insula</td>
<td>right</td>
<td>36 -9 -3</td>
<td>8</td>
<td>3.48</td>
<td>0.912</td>
<td>0.011</td>
</tr>
<tr>
<td>Group x age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostral ACC</td>
<td>left</td>
<td>-3 39 0</td>
<td>7</td>
<td>3.02</td>
<td>0.128</td>
<td>0.043</td>
</tr>
<tr>
<td>dmPFC</td>
<td>right</td>
<td>12 -12 60</td>
<td>37</td>
<td>3.80</td>
<td>0.102</td>
<td>0.004</td>
</tr>
<tr>
<td>Time x age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>left</td>
<td>-9 30 33</td>
<td>13</td>
<td>3.63</td>
<td>0.330</td>
<td>0.036</td>
</tr>
<tr>
<td>Main effect of time</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insula</td>
<td>right</td>
<td>36 -9 -3</td>
<td>25</td>
<td>4.01</td>
<td>0.556</td>
<td>0.008</td>
</tr>
<tr>
<td>T0 Group x age (OCD &gt; HC)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Rostral ACC</td>
<td>right</td>
<td>18 33 9</td>
<td>6</td>
<td>3.62</td>
<td>0.538</td>
<td>0.033</td>
</tr>
<tr>
<td>ACC</td>
<td>right</td>
<td>9 18 27</td>
<td>2</td>
<td>3.15</td>
<td>0.538</td>
<td>0.060</td>
</tr>
<tr>
<td>T1 Group x age (OCD &gt; HC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>left</td>
<td>-9 3 42</td>
<td>22</td>
<td>3.64</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>12 3 48</td>
<td>18</td>
<td>3.44</td>
<td>0.020</td>
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</tr>
<tr>
<td>Insula</td>
<td>right</td>
<td>54 3 0</td>
<td>5</td>
<td>3.26</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>T0T1 OCD x age (T0&lt;T1)</td>
<td></td>
<td></td>
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<tr>
<td>ACC</td>
<td>left</td>
<td>-12 6 45</td>
<td>47</td>
<td>3.98</td>
<td>0.012</td>
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<tr>
<td></td>
<td>right</td>
<td>6 9 45</td>
<td>7</td>
<td>3.30</td>
<td>0.025</td>
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<tr>
<td>Insula</td>
<td>right</td>
<td>27 9 3</td>
<td>36</td>
<td>3.72</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>T0T1 HC x age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No interaction</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
(cont. of table 3)

Correlations between BOLD and age for each group and time point:

<table>
<thead>
<tr>
<th>Region</th>
<th>side</th>
<th>MNI</th>
<th>CS</th>
<th>Z</th>
<th>p(FDR)</th>
<th>p(SVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCD at T0:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rostral ACC</td>
<td>right</td>
<td>9 42 6</td>
<td>19</td>
<td>3.33</td>
<td>0.733</td>
<td>0.005</td>
</tr>
<tr>
<td>OCD at T1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostral ACC</td>
<td>right</td>
<td>6 42 -3</td>
<td>744</td>
<td>4.21</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>dmPFC</td>
<td>right</td>
<td>6 -12 60</td>
<td>45</td>
<td>3.76</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>HC at T0 and T1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

No significant correlation

Correlation between CYBOCS and BOLD in OCD at T0

<table>
<thead>
<tr>
<th>Region</th>
<th>side</th>
<th>MNI</th>
<th>CS</th>
<th>Z</th>
<th>p(FDR)</th>
<th>p(SVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula</td>
<td>right</td>
<td>48 9 -12</td>
<td>5</td>
<td>3.39</td>
<td>0.559</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Correlation between CYBOCS and BOLD in OCD at T1

No significant correlations

Table 3. Imaging results for error trials versus correct trials

Abbreviations: MNI= coordinates of Montreal Neurological Institute, CS= Cluster size, F= F score, Z= Z score, p(FDR)= p value corrected for multiple comparison with the false discover rate method, SVC= small volume correction, dmPFC= dorsomedial prefrontal cortex, dLPFC= dorsolateral prefrontal cortex, ACC= anterior cingulate cortex, SMA= supplemental motor area.

Figure 2.

Figure 2. BOLD signal during error responses versus correct responses in rostral Anterior Cingulate Cortex is positively correlated with age in OCD patients at T0. A) (left panel) BOLD signal in rostral ACC (MNI 9 42 6) (crosshair) B) (middle panel) Scatter plot of age and BOLD signal at T0 in rostral ACC during error responses, in OCD patients; responders in grey, non-responders bold.
Table 4. Main effect of errors vs. correct responses.

<table>
<thead>
<tr>
<th>OCD:</th>
<th>HC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>side</td>
</tr>
<tr>
<td>Insular Cortex, right</td>
<td>39</td>
</tr>
<tr>
<td>Insular Cortex left</td>
<td>-42</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>Medial Gyrus</td>
</tr>
<tr>
<td>Superior gyrus left</td>
<td>-27</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>inferior lobe left</td>
</tr>
<tr>
<td>Supra marginal left</td>
<td>-63, -45, 36; 9</td>
</tr>
<tr>
<td>Parietal cortex inferior lobe right</td>
<td>33, -45, 45; 7</td>
</tr>
<tr>
<td>Precuneus, right</td>
<td>9, -57, 63; 9</td>
</tr>
<tr>
<td>Supra marginal gyrus, right</td>
<td>60, -45, 33; 6</td>
</tr>
<tr>
<td>Temporal lobe, middle gyrus, right</td>
<td>57, -54, 9; 8</td>
</tr>
</tbody>
</table>

Table 4. Main effect of task: BOLD activation after error responses compared to correct responses in OCD and healthy controls before treatment corrected for multiple testing with a p level of < 0.05. Abbreviations: MNI= coordinates of Montreal Neurological Institute, p(FDR)= p value corrected for multiple comparison with the false discover rate method.

Interference analysis, high versus low conflict tasks (table 5):

Group x time x age analysis during high conflict versus low conflict trials showed interaction effects in left anterior insula/operculum, left anterior pole, and trend wise in right insula, i.e. increased activity was associated with age in the OCD group relative to controls. Further analyses showed group x age interaction effects in these regions for OCD patients relative to HC at T0 but not at T1; also, within-group time effects were not significant. Regression analyses revealed in the OCD group a significant linear correlation between age and BOLD signal in bilateral anterior insular cortex during high vs. low conflict trials at T0 but not at T1 (Figure 3A-B). In controls these correlations were absent at both time points. In the anterior pole we found a trend for a correlation between age and BOLD at T1 in OCD patients.

Group x time interaction analyses showed increased BOLD signal in dorsomedial prefrontal cortex, premotor region and ACC in OCD patients relative to controls (Figure 4). Group comparisons at T0 showed relatively decreased BOLD activation in OCD compared to controls in frontal and insular regions, whereas after treatment (T1) increased BOLD activation in OCD patients versus controls was observed in dorsal prefrontal areas and premotor region.
In OCD patients CYBOCS scores at baseline (T0) were positively correlated with BOLD activation of prefrontal middle gyrus. After treatment (T1) we did not find a significant correlation. Changes in symptom severity (delta CYBOCS) in OCD patients did correlate with changes of BOLD signal (T1 versus T0) during incongruent trials versus congruent trials in bilateral dlPFC, dmPFC and precentral regions.

High conflict trials versus low conflict trials at T0 in controls revealed significant activity in left ACC and bilateral insula (table 6). OCD patients showed no significant activations in these regions at our a priori threshold.

Table 5. Imaging results for high conflict versus low conflict

<table>
<thead>
<tr>
<th>Region</th>
<th>side</th>
<th>MNI</th>
<th>CS</th>
<th>Z</th>
<th>p(FDR)</th>
<th>p(SVC)</th>
</tr>
</thead>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>left</td>
<td>-33 24 9</td>
<td>13</td>
<td>3.56</td>
<td>0.775</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>30 18 3</td>
<td>2</td>
<td>3.31</td>
<td>0.775</td>
<td>0.058</td>
</tr>
<tr>
<td>Prefrontal cortex anterior pole</td>
<td>left</td>
<td>-18 63 6</td>
<td>10</td>
<td>3.73</td>
<td>0.775</td>
<td>0.001</td>
</tr>
<tr>
<td>Group x age</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>left</td>
<td>-33 30 27</td>
<td>12</td>
<td>3.42</td>
<td>0.703</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>33 15 3</td>
<td>5</td>
<td>3.36</td>
<td>0.703</td>
<td>0.058</td>
</tr>
<tr>
<td>Prefrontal cortex anterior pole</td>
<td>left</td>
<td>-18 63 6</td>
<td>10</td>
<td>3.73</td>
<td>0.775</td>
<td>0.001</td>
</tr>
<tr>
<td>T0 Group x age (OCD &gt; HC)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>left</td>
<td>-33 30 27</td>
<td>12</td>
<td>3.42</td>
<td>0.703</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>33 15 3</td>
<td>3</td>
<td>3.36</td>
<td>0.703</td>
<td>0.058</td>
</tr>
<tr>
<td>Prefrontal cortex anterior pole</td>
<td>left</td>
<td>-21 63 6</td>
<td>3</td>
<td>3.36</td>
<td>0.703</td>
<td>0.071</td>
</tr>
<tr>
<td>T1 Group x age (OCD &gt; HC)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No interactions</td>
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<tr>
<td>TOT1 HC x age</td>
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<tr>
<td>dmPFC</td>
<td>left</td>
<td>-21 36 57</td>
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</tr>
<tr>
<td></td>
<td>left</td>
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<td>5</td>
<td>3.46</td>
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<tr>
<td>Group x time (Increase of BOLD signal in OCD relative to controls over time)</td>
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<tr>
<td>dmPFC</td>
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<td>-15 3 54,</td>
<td>27</td>
<td>3.73</td>
<td>0.076</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
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<td>55</td>
<td>3.67</td>
<td>0.076</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>30 30 45,</td>
<td>15</td>
<td>3.56</td>
<td>0.076</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>right</td>
<td>51 -6 54,</td>
<td>10</td>
<td>3.38</td>
<td>0.076</td>
<td>0.004</td>
</tr>
<tr>
<td>Premotor</td>
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<td>52</td>
<td>4.79</td>
<td>0.076</td>
<td>0.000</td>
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<tr>
<td></td>
<td>right</td>
<td>36 -18 57,</td>
<td>7</td>
<td>3.40</td>
<td>0.076</td>
<td>0.011</td>
</tr>
<tr>
<td>ACC</td>
<td>left</td>
<td>-9 21 42,</td>
<td>8</td>
<td>3.22</td>
<td>0.076</td>
<td>0.005</td>
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<tr>
<td>OCD&lt;HC at T0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dmPFC</td>
<td>left</td>
<td>-39 24 51</td>
<td>14</td>
<td>3.65</td>
<td>0.234</td>
<td>0.004</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>right</td>
<td>33 -27 27</td>
<td>15</td>
<td>3.63</td>
<td>0.234</td>
<td>0.004</td>
</tr>
<tr>
<td>OCD&gt;HC at T1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFC</td>
<td>right</td>
<td>18 -21 57</td>
<td>39</td>
<td>4.11</td>
<td>0.166</td>
<td>0.012</td>
</tr>
</tbody>
</table>
Correlation BOLD and age for each group and time point:

**OCD at T0**

- **Insula**
  - left: -33 18 3, 12, 3.44, 0.530, 0.007
  - right: 33 15 6, 12, 3.40, 0.530, 0.006

- **Prefrontal cortex anterior pole**
  - left: -21 66 9, 1, 3.10, 0.530, 0.116

**OCD at T1**

- **Prefrontal cortex anterior pole**
  - left: -15 60 9, 6, 3.32, 0.784, 0.060

**HC at T0 and T1**: No significant correlation

**Correlation of BOLD and CYBOCS scores in OCD at T0**

- **dmPFC**
  - left: -42 15 57, 13, 3.64, 0.395, 0.018

At T1 no significant correlation

**Correlations of change in BOLD between T0 and T1 and change in symptom severity in OCD**

- **dlPFC**
  - right: 30 18 57, 43, 4.74, 0.047
  - left: -30 21 66, 14, 3.61, 0.150, 0.015

- **dmPFC**
  - right: 0 45 57, 23, 4.08, 0.145, 0.007

- **Premotor**
  - left: -51 6 54, 10, 3.77, 0.150, 0.016

Table 5. Imaging results showing brain regions with significant different BOLD activations in pediatric OCD patients compared to controls at high conflict trial versus low conflict trials.

**Figure 3. A)**

Figure 3. A correlation of age and BOLD signal during high conflict compared to low conflict trials in bilateral anterior insular cortex in OCD patients was found at T0. A) (left panel) BOLD signal in bilateral insula in OCD patients at T0 correlated with age B) (right panel) Scatter plot of BOLD signal in left insula (MNI -33 18 3) correlated with age in OCD patients responders in grey, non-responders bold.
Table 6.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI</th>
<th>cluster size</th>
<th>Z score</th>
<th>P(FDR)</th>
<th>MNI</th>
<th>cluster size</th>
<th>Z score</th>
<th>P(FDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>-12,3,57</td>
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<td>15</td>
<td>4.29</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula right</td>
<td>42 9 0</td>
<td></td>
<td>17</td>
<td>3.95</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula left</td>
<td>60, 9, 33</td>
<td></td>
<td>5</td>
<td>3.38</td>
<td>0.015</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6
Main effect of task: BOLD activation after high conflict trials versus low conflict trials in OCD and healthy controls before treatment corrected for multiple testing with a p level of < 0.05.
Abbreviations: MNI= coordinates of Montreal Neurological Institute, p(FDR)= p value corrected for multiple comparison with the false discover rate method.

Figure 4.

Figure 4. Interaction effect of group versus time during high conflict versus low conflict tasks show increase of BOLD signal in MedialPFC (cross hairs) and dorsolateral PFC in OCD patients relative to controls over time.
Discussion

In the present study, we investigated response to errors and conflict monitoring during a flanker interference task in a medication free pediatric sample of OCD patients before and after CBT, compared to age and gender matched healthy controls. We demonstrated that in OCD patients activation of the ACC during error monitoring, and the activation of the insula during high conflict trials, was age dependent; also, we could demonstrate treatment effects during high conflict trials.

Behavioral data did not reveal performance differences between patients and controls although both groups performed better (regarding both speed and accuracy) at rescanning. This is in line with previous studies (Fitzgerald et al., 2005; Ursu et al.;2003), which also failed to observe performance differences. Fitzgerald et al. suggested that patients with OCD may have a greater sensitivity to errors (or high conflict trials) reflected by increased BOLD signals. This greater sensitivity may be associated with an increased tendency to perceive errors, even when behavioral demands are adequately met. We suggest that an increased awareness of potential errors in OCD patients is probably reflected in our finding of a positive correlation between performance accuracy and CYBOCS scores.

Imaging data failed to demonstrate interaction effect of group x time for error trials vs. correct trials, indicating that CBT treatment does not affect brain activation patterns during error monitoring. Also, post hoc group comparisons did not reveal significant differences. Whereas committing errors was associated with recruitment of dorsomedial PFC /dorsal ACC and insular cortex in pediatric OCD patients as well as in controls, which is in line with findings in adult OCD populations(60;295), we did not find increased recruitment of rostral ACC in our OCD group, as has been reported for adult OCD patients(60). However, when we included age in the interaction analysis we found an effect in rostral ACC. This greater BOLD response in rostral ACC during error responses was found to be linearly correlated with age in pediatric OCD patients, but not in controls, and this association was also present following treatment. Since we had pooled incongruent and congruent error trials, we performed a post hoc analysis of low conflict errors versus low conflict correct trials which gave similar results (Table 7), so that we may conclude that errors and not incongruent trials gave rise to the above-mentioned results. These findings therefore indicate that although ACC hyperactivity in OCD may be a trait factor, in very young OCD patients the rostral part of the ACC is functioning normally.
Table 7.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI coord.</th>
<th>Cluster</th>
<th>Z score</th>
<th>p(FDR)</th>
<th>p(SVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC rostral part</td>
<td>9 36 6</td>
<td>36</td>
<td>3.29,</td>
<td>0.237</td>
<td>0.016.</td>
</tr>
</tbody>
</table>

*Linear correlation in OCD patients of age and BOLD signal*

ACC rostral part 9 42 6 19 3.33 0.733 0.020. r .633 p 0.001

Table 7. Effect of low conflict error trials versus low conflict correct trials

This explanation is in accordance with the dyspruning hypothesis of Rosenberg and Keshavan (232), proposing differential developmental pathways of various brain areas, resulting in an imbalance in pruning in pediatric OCD patients. These authors observed an age-related volume change of the ACC in controls but not in OCD patients, similarly indicating OCD-related developmental abnormalities in the ACC. In a functional fMRI study, healthy adolescents compared to adults showed less ACC activity during error monitoring (242) from which the authors concluded that the integrated function of the ACC in error monitoring shows a linear progressive developmental specialization. Our data indicate that in OCD patients this development of the ACC is more progressive than in controls, although the reverse explanation, i.e. that the rostral ACC is hypoactive in young OCD patients and normalizes only with increasing age, cannot be ruled out.

When comparing high conflict trials with low conflict trials we found an interaction effect of group x time in dorsomedial prefrontal cortex, premotor region and ACC. This effect was associated with an increase of BOLD in these regions in OCD patients relative to controls. Moreover, these time effects were correlated with change in symptom severity, demonstrating that successful CBT enhances recruitment of these regions during high conflict trials in pediatric OCD patients.

The dorsomedial PFC has been associated with conflict monitoring (329) and an increase of activity in this region could imply greater suppression of a tendency to enact compulsions. The mPFC plays a critical role in regulating affect by changing conditioned associations which are no longer relevant, and by facilitating the voluntary regulation of emotional responses to conditioned or unconditioned stimuli (182). We hypothesize that the increase of mPFC activation reflects the effects of CBT through deconditioning and facilitating voluntary regulation of responses instead of a compulsive, conditioned, reaction pattern.

In addition, we found a group by time by age interaction effect in bilateral insular cortex during high conflict trials. Post-hoc analyses showed that age was linearly correlated to insula activity in the OCD group before but not after treatment, indicating an effect of
treatment only for the older OCD subjects, although these results should be interpreted with caution due to the absence of overall group x time effects in this region. Insular cortex involvement has been reported previously in OCD during symptom provocation paradigms (207), and may reflect increased arousal during high vs. low conflict trials with advancing age in our OCD group, even though state anxiety ratings were not significantly different between groups. We recently reported on increased recruitment of dorsomedial PFC and insula associated with task load of a planning task (Tower of London) in the same pediatric OCD group which normalized after CBT (103). The correlation between accuracy and symptom severity in pediatric OCD patients may be interpreted as increased effort to achieve control in these patients as reflected by the correlations of CYBOCS and BOLD signal in the insula during errors and in dmPFC during high conflict trials. Whereas the correlation with age for the rostral ACC persisted after treatment, the association of insular activity and age ceased to be significant. These findings indicate that abnormal insular activity is a state feature of OCD, in contrast to ACC activity, a suggestion which is in line with results of Hajcak et al (94) who reported no change of error-related negativity after CBT in a pediatric OCD sample.

In conclusion, the present study suggests differential age effects on the developing brain of OCD patients and controls. Although these findings have to be interpreted cautiously, due to the cross-sectional nature of this study, they suggest a different neuronal maturational track in children with OCD compared to healthy children.

Several other potential limitations need to be addressed. First, although our group is reasonably large for an fMRI study, a larger cohort is needed for further investigation of subgroups with regarding to symptom dimensions. Second, our OCD patients differed from controls with regard to intelligence as measured with vocabulary and block design subtests. However, neither score was correlated with overall mean reaction time or accuracy, and a post hoc analysis including WISC block patterns and vocabulary as covariates of non-interest showed similar results, which renders it unlikely that intelligence differences have confounded our results. Also, our groups differed with regard to depression and anxiety ratings as measured using CDI/STAI-C, although self-reported anxiety during scanning was similar. Therefore, the possibility that our results were due, at least in part, to differences in depression ratings cannot be completely ruled out, and needs further investigation.

Third, we did not include a second patient group with e.g. another anxiety disorder so that the specificity of our findings for OCD patients in unclear; also the lack of a placebo OCD group may limit conclusions regarding treatment effects. Finally, it should be noted that most of our results only reached significance, corrected for multiple comparisons, when
applying the small volume correction option in SPM. Whereas this is an accepted method for hypothesis-driven analyses, together with the small cluster sizes of some results it does entail an increased risk of type 1 error.

Notwithstanding these potential limitations, our study is the first to show age-related associations of ACC activity during error monitoring in medication-free pediatric obsessive compulsive disorder patients which persist after successful CBT, and age-related insular activity during high-conflict trials which was found to be state-dependent. In addition, we found treatment effect of CBT during high conflict trials in dmPFC and ACC. Future research should be aimed at further investigating neurodevelopmental aspects of pediatric OCD, preferably in a longitudinal design, and accounting for symptom sub dimensions, to investigate the usefulness of cognitive fMRI paradigms as clinical markers in pediatric OCD.

Key points:

- Error detection and conflict monitoring are seen as central mechanisms in obsessive compulsive disorder (OCD).
- Pediatric OCD patients compared to controls show an age-related increase in rostral ACC activity during error detection, which persisted after cognitive behavioral therapy.
- Pediatric OCD patients show an increase of insular cortex and medial prefrontal cortex activity during high conflict trials after CBT treatment relative to controls. In patients, but not in controls, age is correlated with bilateral insular cortex activation. After treatment this correlation ceased to be significant.
- Both ACC and insula function are therefore to a greater extent age-dependent in pediatric OCD compared to controls; in addition, ACC function may represent a vulnerability factor in OCD, whereas insular function is likely to be a state factor.