Neuropsychological dysfunction in adults with early-onset obsessive-compulsive disorder: the search for a cognitive endophenotype

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Objective: Evidence suggests that early-onset obsessive-compulsive disorder (OCD) is an etiologically distinct subtype of OCD. The objective of the present work was to search for neurocognitive endophenotypes of early-onset OCD based on assessments of attention, memory, and executive function in patients with the disorder and their unaffected siblings.

Methods: We compared the performance of 40 adult patients with early-onset OCD, 40 of their unaffected siblings, and 40 unrelated healthy controls on a neuropsychological battery designed for this study. We searched for associations among test performance, demographic variables (age, sex and years of education) and clinical symptoms of early-onset OCD.

Results: Patients performed significantly worse than healthy controls on the Tower of Hanoi, and the Stroop and Wisconsin tests, indicating impairments in planning, mental flexibility and inhibitory control. The performance of the unaffected first-degree siblings of patients with early-onset OCD on the Stroop and Wisconsin tests also differed from that of healthy controls. Symptom severity in early-onset OCD was strongly correlated with performance on the Tower of Hanoi.

Conclusions: Our findings support the existence of specific executive function deficits in patients with early-onset OCD. Relatives presented an intermediate phenotype between patients and controls, suggesting that executive functions such as mental flexibility and response inhibition may be considered candidate endophenotypes of early-onset OCD.

Keywords: Executive functions; endophenotype; mental flexibility; response inhibition; obsessive-compulsive disorder

Introduction

Obsessive-compulsive disorder (OCD) is a highly heterogeneous condition, whose etiology and pathogenesis are still poorly understood. Dysfunctions in orbitofrontal–striatal circuits have been hypothesized to play a crucial role in the pathophysiology of OCD.1-2 This condition is associated with significant neurocognitive impairment and concomitant functional disability. Neural network abnormalities in both pediatric and adult OCD have been associated with deficits in a variety of cognitive domains, including visuospatial processing abilities, cognitive flexibility, set-shifting and various executive functions.3-7 The primary neuropsychological impairment in OCD lies in executive functions such as working memory, cognitive flexibility, and response inhibition.5,8,9 These deficits have been hypothesized to mediate the relationship between brain dysfunction and clinical symptomatology in patients with OCD.10 This observation is supported by studies which show a direct relationship between anterior cingulate (ACC) activity and cognitive control, since the conflict-monitoring processes in the ACC appear to be involved in the engagement of this cognitive ability.11 The core symptoms of OCD are persistent, obsessive thoughts accompanied by an inability to inhibit the compulsive repetition of behaviors or mental acts. The high demands on conflict-monitoring observed in OCD may lead to ACC dysfunction, resulting in impaired cognitive control. Two meta-analyses have found that the presence of executive impairments in patients with OCD is mainly determined by the integrity of orbitofrontal–striatal circuitry, which includes the orbitofrontal cortex, the striatum and the ACC.12,13 However, it has also been hypothesized that impaired planning capacity in both pediatric7 and adult OCD14 is linked to dysfunctions in dorsolateral-striatal circuitries implicated in the neuro-pathology of OCD, whereas deficits in inhibitory control and cognitive flexibility may be more closely associated with orbitofrontal-striatal pathways.15

Patients with OCD show a bimodal distribution in the age of symptom onset, with an early-onset group centered at 11.1±4.1 years, and a late-onset group centered at 23.5±11.1 years.16,17 Early-onset OCD has
Cognitive endophenotype of OCD

been proposed to be an etiologically distinct subtype of the disorder,18-20 associated with greater symptom severity,20,21 a higher prevalence of tic-related disorders among patients and their first-degree relatives,22-24 a more familial form of the condition,24,25 and a greater prevalence of psychiatry disorders in first-degree relatives26 as compared to late-onset OCD. Tourette syndrome and pervasive developmental disorder are also more likely to co-occur with early-onset OCD, suggesting that neurodevelopmental abnormalities of ventral prefrontal-striatal circuits may contribute to the etiology of both disorders.27 However, it is important to note that, in the present article, “early-onset” was operationalized to mean “onset before age 13” rather than pediatric OCD.

Endophenotypes have been defined as measurable components unseen by the unaided eye located on the continuum between disease and the distal genotype, and which can therefore be found in the unaffected family members of patients with particular disorders at a higher rate than in the general population.28 Endophenotypes are associated with the illness, heritable, and primarily state-independent. With regards to OCD, neuropsychological impairments in executive functioning similar to those displayed by patients with the condition have also been identified in their unaffected first-degree relatives.29-31 Neurocognitive impairments in abilities such as inhibitory control,15,26 set-shifting,15 cognitive flexibility,30,33 planning24 and decision making33 have all been suggested as potential endophenotype markers of OCD. Inhibitory and cognitive flexibility deficits have been found to be mediated by abnormalities in orbitofrontal-striatal circuitry in patients with OCD and their first-degree relatives.15 There is also strong evidence to suggest that familial factors may influence the structural variation of orbitofrontal-striatal brain systems, which are known to be related to inhibitory control deficits.30 Moreover, a longitudinal study has found that executive function deficits in childhood were strongly associated with OCD in adulthood,33 providing further evidence of executive dysfunction as a defining characteristic of OCD. In fact, studies suggest that executive dysfunction may be a trait-like marker of OCD, which has lead researchers to posit such deficits as potential neuropsychological endophenotypes associated with the genetics of the disease.36 The identification of endophenotypes improves the chances of early detection and diagnosis and is therefore particularly important in the case of clinically heterogeneous conditions which vary in comorbidity and age of onset, as is the case of OCD.

Neuropsychological impairments in early-onset OCD have not been widely studied, and it is therefore unclear whether previous research on OCD pathophysiology, which typically combines both early- and late-onset cases, is applicable to this particular form of the condition. Additionally, few studies have examined whether unaffected relatives of patients with early-onset OCD show any disease characteristics which could be considered an endophenotypes for this subtype of disease.

To determine whether the neurocognitive deficits documented in previous OCD research are also present in early-onset cases, we administered a battery of tests to both adult patients with early-onset OCD and healthy unrelated controls so as to examine the following neurocognitive domains: attention, memory, and executive function. To investigate whether these neurocognitive deficits have a familial component, as has been found in other psychiatric disorders, the same battery of tests was also administered to unaffected first-degree siblings of patients with early-onset OCD. Additionally, we evaluated whether any of the neurocognitive deficits observed were related to clinical characteristics such as symptom severity, age, and duration of illness, as well as other features associated with impaired neurocognitive function.

Methods

Subjects

The sample consisted of 40 patients with early-onset OCD (onset age < 13), 40 healthy first-degree siblings, and 40 healthy controls. Recruitment and neuropsychological assessment were performed between May 2012 and June 2013. All subjects were Han Chinese in origin, and aged between 18 and 40 years. Patients with were recruited by local advertisement. Screening procedures included a telephone assessment conducted by two trained psychologist (JZ and QY). Of the 81 subjects who applied for participation, 15 were excluded during telephone screening for having an age of onset greater than age 14, 14 were excluded for not having siblings, three were excluded due to a history of head injury, four due to a comorbid diagnosis of major depressive disorder (MDD) and one due to a history of drug abuse identified during the psychiatric assessment. Of the 44 remaining patients in the sample, four discontinued participation due to an inability to remain without medication during the wash-out period. Control subjects were recruited from staff and students of the South West University. These participants reported no family history of OCD and no previous or current psychiatric disorders in first- and second-degree relatives. Each subject received 100 Chinese Yuan for participation. This study was approved by the Ethics Committee of the South West University, and written informed consent was obtained from all participants.

Two experienced psychiatrists (NL and JW) evaluated patients with OCD using the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).37 Subjects had no other Axis I comorbidities. All patients underwent a 4-week washout period from medication and psychotherapy before the study. At the start of the study, the same two psychiatrists assessed patients using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the 14-item Hamilton Anxiety Rating Scale (HARS), and the 17-item Hamilton Depression Rating Scale (HDRS). The presence and severity of tics were determined via interview and using the Yale Global Tic Severity Scale (YGTSS).38 Any siblings of OCD patients and healthy controls with a prior psychiatric diagnosis were excluded from the sample, as were participants with a history of intellectual disability, neurological illness, brain injury or trauma, or drug or alcohol abuse.
Neuropsychological measurement

The following neuropsychological tests were administered to all participants during one session, which lasted approximately 1 hour and 30 minutes:

Attention tests

The digit span test (forward and backward) from the Wechsler Memory Scale (WMS) III was used to evaluate attention span. The Trail Making Test (TMT) (times needed to complete task A and B) was used to evaluate attention (part A) and attention and psychomotor speed (part B).

Memory tests

The Logical Memory (LM) subtest of the WMS III assesses the immediate (LM1) and 30-minute delayed recall (LM2) of two stories told by a psychologist, while the Visual Reproduction (VR) test measures the number of details in two geometric figures which patients can recall both immediately (VR1) and after a delay (VR2).

Executive function tests

The Stroop Color Naming and Color/Word Interference test measures selective attention and response inhibition. The Tower of Hanoi (TOH) test measures planning and decision-making abilities. Subjects must solve problems with the fewest possible steps as quickly as possible while following certain rules.

Statistical analyses

Statistical analyses were carried out using SPSS version 17.0 for Windows. The sociodemographic characteristics of OCD patients, siblings and healthy controls were compared using chi-square analyses. Between-group comparisons of continuous variables were performed using univariate analysis of variance (one-way ANOVA). Significant ANOVAs were followed by Fisher’s least significant difference (LSD) post-hoc test. The cognitive performance of OCD patients with and without tics was compared using Student’s t-test.

Pearson correlations were performed to analyze the relationship between performance on the three executive function tests and the severity of OCD symptoms (Y-BOCS scores) or clinical characteristics which may influence cognitive performance (duration of illness, HARS scores, and HDRS scores). Differences were considered significant if p < 0.05.

Results

Demographic characteristics

The demographic characteristics of the three study groups are shown in Table 1. Twenty-six patients (65%) had tics. The distribution of YGTSS scores (range: 0-50) in the OCD group was as follows: 14 patients obtained a score of 0 (n=14), 16 obtained scores between 1 and 9 (n=16), and 10 scored between 10 and 19. Three of the OCD patients without tics had such symptoms during adolescence. Patients with and without tics did not differ on any neuropsychological test. All patients were exclusively right-handed. Additionally, OCD patients, their siblings and healthy controls did not differ in terms of age (F = 1.91, df = 2, 117, p = 0.152), gender (χ² = 0.46, df = 2, p = 0.79) or years of education (F = 1.095, df = 2, 117, p = 0.339).

Neuropsychological measures

Table 2 shows the neuropsychological test results of patients, healthy siblings and controls. A one-way ANOVA revealed significant between-group differences on the Stroop test and the WCST. Group differences on the Stroop test were observed on the Stroop Color Naming (F = 26.57, df = 2, 117, p < 0.001) and Color/Word Interference conditions (F = 26.16, df = 2, 117, p < 0.001). Significant group differences were also observed in the number of categories (F = 9.64, df = 2, 117, p < 0.001), perseverative errors (F = 7.39, df = 2,117, p = 0.001) and non-perseverative errors (F = 11.76, df = 2, 117, p < 0.001) on the WCST. Groups differed significantly on the TOH (F = 3.576, df = 2, 117, p = 0.031), which evaluates planning and decision-making abilities. However, no significant effects were identified on memory tests or the TMT.

Post-hoc comparisons revealed that patients with OCD and their first-degree siblings showed significantly poorer response inhibition on the Stroop test than controls, and made significantly more category, perseverative and non-perseverative errors on the WCST. However, patients and their siblings did not differ from each other on any of the tests administered. Lastly, patients with OCD showed worse performance than controls on the TOH (p = 0.026).

Correlation between neuropsychological performance and clinical symptoms

Pearson correlation analysis showed a strong relationship between TOH performance and Y-BOCS scores in adults with early-onset OCD (r = -0.548, p = 0.009, two-tailed). No significant associations were identified between Y-BOCS scores and performance on the WCST or Stroop test.

Discussion

The aim of the present study was to investigate neuropsychological performance in adults with early-onset OCD, their unaffected first-degree siblings and unrelated healthy controls with no family history of OCD. Our study revealed that both patients with OCD and their healthy relatives...
performed significantly worse than controls on the WCST and Stroop test. To our knowledge, this is the first study to report executive dysfunction in the unaffected relatives of patients with early-onset OCD. We suggest that executive dysfunction, particularly in the areas of mental flexibility and response inhibition, may be common to both adults with early-onset OCD and their unaffected siblings. Furthermore, our findings suggested that the severity of early-onset OCD symptoms is associated with impairments in planning ability.

The patients with early-onset OCD in the present sample showed poorer cognitive flexibility than controls, as indicated by their tendency to make more perseverative and non-perseverative errors and complete fewer categories on the WCST. These findings corroborate reports of impaired cognitive flexibility in pediatric OCD. Studies have found, for instance, that pediatric patients with OCD were slower to complete a set-shifting task than healthy controls, in addition to and making significantly more errors and completing fewer categories on the WCST than healthy participants of the same age. These results, together with the present study, suggest that early-onset OCD is associated with impairments in mental set-shifting and non-verbal abstract concept formation. MRI studies have also found that set-shifting deficits in pediatric OCD were accompanied by lower frontal-striatal activation than that observed in healthy controls.

Whether late-onset OCD is also associated with deficits in cognitive flexibility is still unclear, since previous studies of this cognitive process tend to evaluate mixed patient populations containing individuals with both

### Table 1
Demographic and clinical characteristics of the three participant groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early-onset OCD (n=40)</th>
<th>Siblings (n=40)</th>
<th>Controls (n=40)</th>
<th>F (df = 2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.4 ± 4.8</td>
<td>25.3 ± 6.4</td>
<td>25.4 ± 5.9</td>
<td>1.91</td>
<td>0.152</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.1 ± 2.7</td>
<td>12.5 ± 2.5</td>
<td>13.5 ± 2.4</td>
<td>1.095</td>
<td>0.339</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender (men:women)</td>
<td>23:17</td>
<td>20:20</td>
<td>21:19</td>
<td>0.46*</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Clinical characteristics

| Age at onset           | 10.5 ± 1.9             |
| Illness duration (years)| 12.5 ± 4.8             |
| Y-BOCS score           | 24.2 ± 3.6             |
| HARS score             | 10.4 ± 1.7             |
| HDRS score             | 11.1 ± 2.3             |
| YGTSS score            | 12.2 ± 6.5 (n=26)      |

Data expressed as mean ± standard deviation, unless otherwise stated.
* df = degrees of freedom; HARS = 14-item Hamilton Anxiety Rating Scale; HDRS = 17-item Hamilton Depression Rating Scale; OCD = obsessive-compulsive disorder; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; YGTSS = Yale Global Tic Severity Scale.

### Table 2
Neurocognitive test scores for patients, siblings and controls

<table>
<thead>
<tr>
<th>Test</th>
<th>OCD (mean ± SD)</th>
<th>Siblings (mean ± SD)</th>
<th>Controls (mean ± SD)</th>
<th>F (df = 2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span (T)</td>
<td>21.13 ± 1.76</td>
<td>21.45 ± 1.34</td>
<td>21.75 ± 1.98</td>
<td>0.23</td>
<td>0.796</td>
</tr>
<tr>
<td>Forward</td>
<td>12.55 ± 0.98</td>
<td>12.5 ± 0.84</td>
<td>12.4 ± 1.17</td>
<td>2.03</td>
<td>0.136</td>
</tr>
<tr>
<td>Backward</td>
<td>8.65 ± 1.82</td>
<td>9.03 ± 1.29</td>
<td>9.4 ± 1.82</td>
<td>1.33</td>
<td>0.268</td>
</tr>
<tr>
<td>TMT (sec.)</td>
<td>32.67 ± 3.19</td>
<td>33.69 ± 3.29</td>
<td>34.87 ± 5.49</td>
<td>2.83</td>
<td>0.063</td>
</tr>
<tr>
<td>WCST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>4.35 ± 1.44</td>
<td>4.73 ± 1.26</td>
<td>5.5 ± 0.78</td>
<td>9.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Per Err</td>
<td>13.2 ± 6.06</td>
<td>11.88 ± 5.91</td>
<td>8.38 ± 5.41</td>
<td>7.39</td>
<td>0.001</td>
</tr>
<tr>
<td>NPer Err</td>
<td>20.4 ± 6.64</td>
<td>18.15 ± 7.05</td>
<td>13.2 ± 6.68</td>
<td>11.76</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroop-C</td>
<td>107.6 ± 2.82</td>
<td>108.43 ± 2.83</td>
<td>111.33 ± 1.16</td>
<td>26.57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroop-CW</td>
<td>106.75 ± 1.93</td>
<td>107.62 ± 2.86</td>
<td>110.15 ± 1.56</td>
<td>26.56</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tower of Hanoi</td>
<td>51.83 ± 9.48</td>
<td>54.45 ± 5.56</td>
<td>56.48 ± 7.88</td>
<td>3.57</td>
<td>0.031</td>
</tr>
<tr>
<td>LM1</td>
<td>8.3 ± 1.57</td>
<td>7.65 ± 2.3</td>
<td>8.88 ± 3.11</td>
<td>2.53</td>
<td>0.084</td>
</tr>
<tr>
<td>LM2</td>
<td>5.9 ± 1.77</td>
<td>5.3 ± 2.4</td>
<td>6.48 ± 2.42</td>
<td>2.82</td>
<td>0.064</td>
</tr>
<tr>
<td>VR1</td>
<td>23.0 ± 1.54</td>
<td>23.3 ± 0.79</td>
<td>23.65 ± 1.27</td>
<td>2.76</td>
<td>0.067</td>
</tr>
<tr>
<td>VR2</td>
<td>21.3 ± 1.86</td>
<td>21.6 ± 1.58</td>
<td>22.03 ± 1.57</td>
<td>2.88</td>
<td>0.060</td>
</tr>
</tbody>
</table>

ANOVA between groups

<table>
<thead>
<tr>
<th>Test</th>
<th>OCD vs. controls</th>
<th>OCD vs. siblings</th>
<th>Siblings vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span (T)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
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<tr>
<td>Backward</td>
<td></td>
<td></td>
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<tr>
<td>TMT (sec.)</td>
<td></td>
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<tr>
<td>WCST</td>
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</tbody>
</table>

p-values for comparisons

Cat = categories; df = degrees of freedom; LM1 = logical memory, immediate recall; LM2 = logical memory, delayed recall; NPer Err = non-perseverative errors; OCD = obsessive-compulsive disorder; Per Err = perseverative errors; SD = standard deviation; TMT = Trail Making Tests A and B; VR1 = visual reproduction, immediate recall (WMS); VR2 = visual reproduction, delayed recall; WCST = Wisconsin Card Sorting Test.
* Adjusted for sociodemographic variables (sex, educational level, age at assessment).
early- and late-onset disease. Not surprisingly, these studies have yielded inconsistent results. Some have reported impaired mental set-shifting in OCD patients relative to healthy controls,\textsuperscript{45,46} while others have identified no such impairments.\textsuperscript{47,48}

These results suggest that, as in the case of pediatric OCD, adults with the early onset form of the disorder may also have deficits in cognitive flexibility. Some executive impairments may be state independent in early onset OCD. However, these findings should be interpreted with caution since all patients in the present study were medicated and most presented with symptom recurrence after the wash-out period. Therefore, cognitive performance in our sample may have been worse than that reported in other similar studies, and differences between subjects may have been more evident.

Adults with early-onset OCD also showed significantly lower response inhibition on the Stroop Color Naming Test and Word/Color Interference Test than healthy controls. This is consistent with previous reports suggesting that children with OCD show impaired performance in oculomotor tests of response inhibition.\textsuperscript{49,50}

Impairments in the inhibitory control of patients with pediatric OCD have also been detected in a multi-source interference task,\textsuperscript{51} during which patients failed to exhibit either post-error slowing or post-conflict adaptation of cognitive control. A similar loss of interference control has been reported in studies involving mixed samples of adults with early- and late-onset disease.\textsuperscript{29,52} The inability to inhibit repetitive thoughts or behaviors may explain the repetitive intrusive thoughts and compulsive behaviors which characterize OCD according to the DSM-IV. This impairment in response inhibition may lead patients with early-onset OCD to be less successful than those with late-onset disease at controlling intrusive thoughts (obsessions) and behaviors.

In addition to impairments in cognitive flexibility and response inhibition, our adult patients with early-onset OCD performed poorly on the TOH, suggesting impairments in planning and decision-making abilities. These findings are consistent with previous studies. An fMRI study found that pediatric patients with OCD performed a planning task significantly more slowly than healthy controls, albeit with similar accuracy, indicating impairments in planning ability.\textsuperscript{7} Patients with OCD may be slower at such tasks because they spend more time checking for errors and generating alternative responses when such an error is found.\textsuperscript{53} Our findings showed that individuals with early-onset OCD were slower than healthy controls even in the simpler problems on the TOH, suggesting significant difficulty facing novel situations.

Perhaps the most striking contribution of the present study was the finding that unaffected first-degree relatives of adult patients with early-onset OCD share many of the executive function deficits observed in the patients themselves. First-degree relatives performed significantly worse than healthy controls on the Stroop test and the WCST, suggesting that impaired cognitive flexibility and response inhibition may be trait markers for early-onset OCD which contribute to, rather than result from, the clinical symptoms of OCD. We also observed a strong negative correlation between performance on the TOH and symptom severity in adults with early-onset OCD. First-degree siblings did not appear to share all the executive function deficits of patients with early-onset OCD. This suggests that inhibitory control and flexibility, but not planning, may be considered part of the endophenotype of early-onset OCD.

Previous studies of unaffected first-degree relatives of adult patients with OCD have reported cognitive deficits in various domains, such as planning,\textsuperscript{55} response inhibition, set-shifting,\textsuperscript{30} and decision-making.\textsuperscript{31} While it is reassuring that our findings in early-onset OCD were similar to those obtained in earlier studies, comparisons between these findings should be made with caution, since earlier studies involved mixed samples of patients with early- and late-onset OCD. The success of our approach suggests that future studies can and should analyze the two subtypes of the disorder separately. Nevertheless, our results, together with those of previous studies, suggest that specific executive traits can be used as endophenotypes to dissect the genetic complexity of early-onset OCD.

The present study was the first to demonstrate familial resemblance in the performance of cognitive flexibility and response inhibition tests, but not in other measures of executive function such as Digit Span Backward, TOH, and TMT-Part B, which rely on abilities such as working memory, planning and executive control. This could be related to the fact that current data do not support the involvement of working memory and planning impairments in the endophenotype of adult early-onset OCD, since these abilities rely on dorsolateral frontal loops which are not as closely associated with the etiology of OCD. Additionally, we could not rule out all moderator variables known to influence cognition functions, such as chronicity of the disease, medication effects and symptom relapse after wash-out. In summary, our findings suggested that impairments in executive functions such as cognitive flexibility and response inhibition may be endophenotypic markers of early-onset OCD. Future studies should examine larger samples of patients and relatives, and perhaps combine neuropsychological assessments with imaging and genetic approaches, in order to elucidate the pathophysiology of early-onset OCD and its relationship to the late-onset form of the condition.

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Disclosure

The authors report no conflicts of interest.

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