Symptom-Based Profiling and Multimodal Neuroimaging of a Large Preteenage Population Identifies Distinct Obsessive-Compulsive Disorder–like Subtypes With Neurocognitive Differences

Xinran Wu, Gechang Yu, Kai Zhang, Jianfeng Feng, Jie Zhang, Barbara J. Sahakian, and Trevor W. Robbins

ABSTRACT
BACKGROUND: Obsessive-compulsive disorder (OCD) is characterized by both internalizing (anxiety) and externalizing (compulsivity) symptoms. Currently, little is known about their interrelationships and their relative contributions to disease heterogeneity. Our goal is to resolve affective and cognitive symptom heterogeneity related to internalized and externalized symptom dimensions by determining subtypes of children with OCD symptoms, and to identify any corresponding neural differences.

METHODS: A total of 1269 children with OCD symptoms screened using the Child Behavior Checklist Obsessive-Compulsive Symptom scale and 3987 matched control subjects were obtained from the Adolescent Brain Cognitive Development (ABCD) Study. Consensus hierarchical clustering was used to cluster children with OCD symptoms into distinct subtypes. Ten neurocognitive task scores and 20 Child Behavior Checklist syndrome scales were used to characterize cognitive/behavioral differences. Gray matter volume, fractional anisotropy of major white matter fiber tracts, and functional connectivity among networks were used in case-control studies.

RESULTS: We identified two subgroups with contrasting patterns in internalized and externalized dimensions. Group 1 showed compulsive thoughts and repeated acts but relatively low anxiety symptoms, whereas group 2 exhibited higher anxiety and perfectionism and relatively low repetitive behavior. Only group 1 had significant cognitive impairments and gray matter volume reductions in the bilateral inferior parietal lobe, precentral gyrus, and precuneus gyrus, and had white matter tract fractional anisotropy reductions in the corticostriatal fasciculus.

CONCLUSIONS: Children with OCD symptoms are heterogeneous at the level of symptom clustering and its underlying neural basis. Two subgroups represent distinct patterns of externalizing and internalizing symptoms, suggesting that anxiety is not its major predisposing factor. These results may have implications for the nosology and treatment of preteenage OCD.

https://doi.org/10.1016/j.bpsc.2021.06.011

Obsessive-compulsive disorder (OCD) is one of the few psychiatric disorders with both internalizing (such as anxiety, worries, and obsessions) and externalizing (compulsivity and repetitive behaviors) symptoms (15). Previous theoretical models of OCD have posited that anxiety has a close relationship with compulsive behavior, which hypothetically causes its reduction according to a negative reinforcement account (16–18). Although OCD has been removed from the traditional DSM category of anxiety disorders and placed in its own classification of obsessive-compulsive and related disorders, the debate continues about the precise relationship of anxiety and compulsivity in OCD (19–21). Delineating clinically distinct OCD subtypes may help to resolve this issue and is also important in understanding the nosology and psychopathologic and effective treatment of OCD is one of the few psychiatric disorders with both internalizing (such as anxiety, worries, and obsessions) and externalizing (compulsivity and repetitive behaviors) symptoms (15). Previous theoretical models of OCD have posited that anxiety has a close relationship with compulsive behavior, which hypothetically causes its reduction according to a negative reinforcement account (16–18). Although OCD has been removed from the traditional DSM category of anxiety disorders and placed in its own classification of obsessive-compulsive and related disorders, the debate continues about the precise relationship of anxiety and compulsivity in OCD (19–21). Delineating clinically distinct OCD subtypes may help to resolve this issue and is also important in understanding the nosology and psychopathologic and effective treatment of OCD is one of the few psychiatric disorders with both internalizing (such as anxiety, worries, and obsessions) and externalizing (compulsivity and repetitive behaviors) symptoms (15). Previous theoretical models of OCD have posited that anxiety has a close relationship with compulsive behavior, which hypothetically causes its reduction according to a negative reinforcement account (16–18). Although OCD has been removed from the traditional DSM category of anxiety disorders and placed in its own classification of obsessive-compulsive and related disorders, the debate continues about the precise relationship of anxiety and compulsivity in OCD (19–21). Delineating clinically distinct OCD subtypes may help to resolve this issue and is also important in understanding the nosology and psychopathologic and effective treatment of OCD is one of the few psychiatric disorders with both internalizing (such as anxiety, worries, and obsessions) and externalizing (compulsivity and repetitive behaviors) symptoms (15). Previous theoretical models of OCD have posited that anxiety has a close relationship with compulsive behavior, which hypothetically causes its reduction according to a negative reinforcement account (16–18). Although OCD has been removed from the traditional DSM category of anxiety disorders and placed in its own classification of obsessive-compulsive and related disorders, the debate continues about the precise relationship of anxiety and compulsivity in OCD (19–21). Delineating clinically distinct OCD subtypes may help to resolve this issue and is also important in understanding the nosology and psychopathologic and effective treatment of OCD is one of the few psychiatric disorders with both internalizing (such as anxiety, worries, and obsessions) and externalizing (compulsivity and repetitive behaviors) symptoms (15). Previous theoretical models of OCD have posited that anxiety has a close relationship with compulsive behavior, which hypothetically causes its reduction according to a negative reinforcement account (16–18). Although OCD has been removed from the traditional DSM category of anxiety disorders and placed in its own classification of obsessive-compulsive and related disorders, the debate continues about the precise relationship of anxiety and compulsivity in OCD (19–21). Delineating clinically distinct OCD subtypes may help to resolve this issue and is also important in understanding the nosology and psychopathologic and effective treatment of
OCD. Traditional subtype studies have focused on specific symptoms of obsessive-compulsive behavior (such as harming, hoarding, contamination, and symmetry) (5,22–24). However, these studies have been mostly behavioral, have been based on small samples, and did not conduct structural and functional neuroimaging studies to identify neural correlates based on small samples, and did not conduct structural and functional neuroimaging studies to identify neural correlates associated with specific symptom dimensions or subtypes (8,9,25).

Considering the reported high level of heterogeneity in OCD patients (4,5,26) and the core motivational domains of symptoms involving obsession, compulsivity, and anxiety, we expected that distinct subtypes would be identified based on symptomatic clustering, which may show different levels of repetitive behavior, obsession, and psychological anxiety. In this study, a large adolescent sample (1269 children with OCD symptoms, 3987 control subjects) from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org/) was used to investigate neural and behavioral heterogeneity of pediatric OCD. These children with OCD-like symptoms may not necessarily meet the diagnostic criteria for OCD but usually show high compulsion and obsession, and therefore can be regarded as a subhealth group. In this study, we adopted a clustering-based analysis using the Child Behavior Checklist (CBCL) Obsessive-Compulsive Symptom (OCS) scale (involving 10 transdiagnosis dimensions such as obsession, compulsivity, fear, anxiety, and perfectionism) in conjunction with structural and functional neuroimaging and cognitive analysis to identify distinct neural correlates of these subgroups and their cognitive impairments.

METHODS AND MATERIALS

Participants

The study sample included 11,878 children 9 to 10 years of age recruited from 22 research sites across the United States from the ABCD Study data release (version 3.0, November 2020), which included the clinical, behavioral, cognitive, and multimodal neuroimaging data from the baseline, 1-year follow-up, and 2-year follow-up assessments.

Table 1. OCS Scale Items From the CBCL

<table>
<thead>
<tr>
<th>CBCL Item</th>
<th>Question</th>
<th>OCS-2</th>
<th>OCS-6</th>
<th>OCS-8</th>
<th>OCS-11</th>
</tr>
</thead>
<tbody>
<tr>
<td>#9</td>
<td>Can’t get mind off thoughts</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(obsession)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#31</td>
<td>Fears doing bad</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#32</td>
<td>Must be perfect</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#45</td>
<td>Nervous, tense</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>#50</td>
<td>Fearful, anxious</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>#52</td>
<td>Feels too guilty</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>#66</td>
<td>Repeats acts (compulsion)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>#84</td>
<td>Strange behavior</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>#85</td>
<td>Strange ideas</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#99*</td>
<td>Too concerned with neatness</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>or cleanliness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#112</td>
<td>Worries</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

*The number in the first column represents the serial number of the item in the CBCL. The letter “x” indicates that the item is included in the version of the OCS scale.

CBCL: Child Behavior Checklist; OCS, Obsessive-Compulsive Symptom.

*#99 was removed from the 2001 revision of the CBCL.

Distinct OCD-like Subtypes With Cognitive Differences

Diagnosis of Children With OCD-like Symptoms by the CBCL OCS Scale

The CBCL is a parent-reported questionnaire in widespread use to measure behavioral problems for school-aged children (27–29) in large-scale population studies such as the ABCD Study (30,31). The OCS scale is a subset of the CBCL items that is associated with OCD symptoms, which has been shown to be effective in distinguishing subjects with OCD from subjects without OCD (32–34) and demonstrates good internal consistency and longitudinal stability (33,35). There are four OCS scale versions extracted from CBCL, named OCS-2, OCS-6, OCS-8, and OCS-11 and containing several overlapping subitems (Table 1) (32). We used the best cutoff scores of each of these three scales recommended by Andersen and Bilenberg (34) to screen children with OCD-like symptoms (OCS-2 ≥ 2, OCS-6 ≥ 4, or OCS-8 ≥ 6). Specifically, we aggregated the patients diagnosed from each of these three OCS scale versions (i.e., we took their union). The diagnostic overlap among these three scale versions was 86%, 66%, and 60% (pairwise overlap), respectively, indicating high consistency. OCS-11 was not used, as item #99 (too concerned with neatness or cleanliness) was excluded in the current CBCL, and therefore the cutoff score for OCS-11 is not applicable. A total of 1269 children (10.69% of all participants) were confirmed as children with OCD-like symptoms.

The healthy control (HC) group was defined by the OCS scale and the parent-completed, computerized version of Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version (which provides children’s DSM-5 diagnoses). All subjects who were diagnosed as children with OCD-like symptoms and/or any mental disorder by the Kiddie Schedule for Affective Disorders and Schizophrenia–Present Version were excluded, and 3987 children finally remained in the HC group.

Consensus Clustering of the Multidimensional OCS Scale

The OCS scale contains altogether 10 different items covering wide phenotypic expressions and different psychological
Distinct OCD-like Subtypes With Cognitive Differences

features of OCD, including core symptoms of OCD (i.e., #9 [obsession], #66 [compulsion]) and other OCD-related symptoms such as anxiety (#45, #50, #52, #112) and perfectionism (#32) (21,36,37), allowing dimensional psychiatry approaches (38) such as reliable subtyping to be implemented.

All 10 items of OCS scale were put into consensus hierarchical clustering algorithm (ConsensusClusterPlus package, R version 4.0.0 [R Foundation for Statistical Computing, Vienna, Austria]) (39), a bootstrapping approach widely used in pathology and neuroscience (40-42) to identify subtypes. It involves 1000 iterations of the clustering algorithm with 80% random resampling of the predefined k (number of clusters), and a subject × subject co-consistency matrix was generated wherein each element equals 1 if 2 individuals were classified into the same cluster and 0 otherwise in each iteration. Co-consistency matrices across 1000 iterations were integrated for each k to generate a consensus matrix reflecting the frequency of individuals being assigned to the same cluster. Agglomerative hierarchical clustering of consensus matrices with k ranging from 2 to 10 was then adopted. Euclidean distance was used. Three statistics, silhouette (average silhouette width), wss (total within sum of squares), and gap_stat (gap distance) was used to determine the optimal k (nbclust function of cluster package) (43). In addition, we also performed a nonhierarchical clustering (k-means) analysis for validation of the consensus hierarchical clustering.

Behavioral and Neuroimaging Differences Between Subgroups and HC Group

We compared the neurocognitive abilities, CBCL subscales, and neuroimaging measures between the different subgroups and the HC group. Ten cognitive ability scores from the National Institutes of Health toolbox cognition battery and scores of 20 syndrome scales from the CBCL were used to characterize the cognitive and behavioral profile of different subtypes (44) (see Supplemental Methods in Supplement 1).

For neuroimaging measures, we compared the gray matter volume of 68 cortical regions (Desikan parcellation) (45) and 17 subcortical regions (automatic subcortical segmentation) (46), tract-averaged fractional anisotropy (FA) of 37 white matter tracts (AtlasTrack) (47), and resting-state functional connectivity (RSFC) among 13 subnetworks (Gordon atlas) (48) between patients of different subtypes and HC subjects (see Supplemental Methods in Supplement 1 for more details). Linear mixed models (LMMs) (fitlm function of MATLAB R2018b [The MathWorks, Inc.]) were used to evaluate intergroup differences, which included the categorical variables of subject group, sex, age, race, body mass index, puberty, and family structures nested within site (or magnetic resonance imaging device serial number) as random effect variables (49).

For a contrast between one subgroup and HC, if the subject belonged to the subgroup, the variable was equal to 1; if the subject belonged to the HC group, the variable was equal to 0. Those subjects belonging to other subgroups were removed. For gray matter volume, intracranial volume was included as a covariate; for RSFC, mean framewise displacement during scanning was additionally included; and for FA, average framewise motion was included. For each predictor, the LMM provides t-test results for the regression coefficient and a p value indicating significance. The false discovery rate (FDR) (q = .05) was used to correct for multiple comparisons.

Association Between Neural Differences, Psychiatric Symptoms, and Cognitive Ability

We used LMMs to investigate the associations between neuroimaging measures with significant differences in subgroups and CBCL syndrome scales/cognitive ability using all 11,878 participants. The predictive variable was each of the items from CBCL syndrome scales and National Institutes of Health task scores, and the dependent variable was each neuroimaging feature. The same covariates were used in the analysis as in the intergroup difference analysis.

Sensitivity Analysis

To validate the robustness of our results, the following sensitivity analyses were performed. First, a split-half cross-site validation was performed by assigning all data to two halves (part 1 and part 2) and repeating the above analysis on each half. Second, to control the effect of intelligence, we added intelligence score (total computed intelligence of National Institutes of Health Cognition Battery) as a fixed effect to the model and re-fit our neuroimaging analysis in groups 1 and 2 (G1 and G2). Third, we repeated our neuroimaging analysis in G1, controlling for the effect of attention-deficit/hyperactivity disorder (ADHD), a common comorbidity with OCD (50-52), as G1 showed higher attention deficits. Fourth, similarly, a paired t-test for behavioral phenotype between G2 and HC after removing the anxiety disorder children was performed, to reduce the confounding effect of anxiety comorbidity because G2 showed anxiety-like characteristics (see Supplemental Methods and Supplemental Results in Supplement 1).

Longitudinal Analysis

Using ABCD Study follow-up data, we investigated whether the two subgroups remained stable over time and development in terms of cognitive and psychiatric patterns. Moreover, we also examined whether neuroimaging alterations at baseline could predict behavioral phenotypes after 2 years’ development by LMM (see Supplemental Methods in Supplement 1).

RESULTS

Two Stable Subtypes With Contrasting Patterns in Symptoms of Compulsivity and Anxiety

Consensus hierarchical clustering of the multidimensional symptom profiles of children with OCD-like symptoms revealed two subtypes (Figure 1 and Table 2). The optimal k = 2 was determined by average silhouette coefficient (Figure S8 in Supplement 1). Of the two subtypes, G1 mainly showed compulsive thoughts and repeated acts but with low anxiety, and G2 showed high perfectionism, high anxiety, and relatively less repeated behavior and compulsion.
Cognitive Impairments and Behavioral Differences of Two OCD-like Subtypes

G1 showed significantly lower general cognitive ability than G2 and the HC group (total computed intelligence \( t_{3967} = -10.73, p = 1.54 \times 10^{-20} \)), while G2 showed intelligence comparable to the HC group \( t_{3967} = 1.65, p = .1 \) but with higher scores in the picture vocabulary task \( t_{3967} = 3.93, p = 8.69 \times 10^{-5} \) in the reading task \( t_{3967} = 2.22, p = 2.63 \times 10^{-5} \) and for crystallized intelligence \( t_{3967} = 3.52, p = 4.4 \times 10^{-5} \) (Figure 2B).

Both OCD-subtype subjects showed significantly higher total OCS scale score than the HC subjects (G1 vs. HC \( t_{1266} = 95.7, p < 1 \times 10^{-200} \), G2 vs. HC \( t_{1266} = 110.7, p < 1 \times 10^{-200} \)), with G2 showing higher total score than G1 (G1 vs. G2 \( t_{1266} = -10.04, p = 7.03 \times 10^{-23} \)). G1 showed a higher CBCL total problem syndrome score than G2 (G1 vs. G2 \( t_{1266} = 3.36, p = .0008 \)). For other psychiatric symptoms, the most obvious trend was for G1 to show a more pronounced externalized syndrome score (G1 vs. G2 \( t_{1266} = 7.1, p = 2.05 \times 10^{-4} \)) while G2 showed a prominent internalized syndrome score (G1 vs. G2 \( t_{1266} = -11.8, p = 1.4 \times 10^{-30} \)). Specifically, G1 mainly showed higher scores in attentional deficits, ADHD-related syndrome, conduct problems, and thought problems; in comparison, G2 mainly showed a higher level of internalized symptoms, such as anxious/depressed, anxiety disorder, and OCD syndrome scale score in the CBCL (Figure 2A; Table S17 in Supplement 2).

Distinct Anatomical and Functional Differences in the Two OCD-like Subtypes

We found significantly decreased intracranial volume in G1 compared with the HC group \( t_{4378} = -3.03, p = 2.45 \times 10^{-5} \). The volume of the bilateral precentral gyrus (left/right \( t_{4378} = -3.76, p = 1.7 \times 10^{-4} \)), bilateral inferior parietal lobe (IPL) (left/right \( t_{4378} = -3.47, p = 5.2 \times 10^{-5} \)), bilateral inferior temporal lobe (left/right \( t_{4378} = -3.87, p = 1.1 \times 10^{-4} \), bilateral precuneus \( t_{4378} = -8.69, p = 1.17 \times 10^{-4} \), FDR \( q < .01 \)) also decreased significantly in G1. G1 also showed extensive reductions in FA of white matter tracts, especially the bilateral superior corticostriatal tract (SCS) (connecting the superior frontal/parietal cortex and striatum; left SCS \( t_{4342} = 4.56, p = 2.45 \times 10^{-4} \), right SCS \( t_{4342} = 3.03, p = 7.6 \times 10^{-3} \))

Table 2. Demographic Information of HC Subjects and the Two Subtypes of Children With OCD (G1 and G2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC Group (n = 3987)</th>
<th>G1 (n = 909)</th>
<th>G2 (n = 360)</th>
<th>t (G1 – G2) (df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2132</td>
<td>286</td>
<td>187</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age, Months, Mean ± SD</td>
<td>119.1 ± 7.5</td>
<td>119.1 ± 7.6</td>
<td>118.8 ± 7.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Can’t Get Mind Off Thoughts (Obsession)</td>
<td>0.11</td>
<td>1.42</td>
<td>1.06</td>
<td>9.81 (633.5)</td>
<td>5.88 \times 10^{-22}</td>
</tr>
<tr>
<td>Fears Doing Bad</td>
<td>0.03</td>
<td>0.27</td>
<td>0.90</td>
<td>-19.35 (633.5)</td>
<td>2.91 \times 10^{-73}</td>
</tr>
<tr>
<td>Must Be Perfect</td>
<td>0.20</td>
<td>0.54</td>
<td>1.39</td>
<td>-20.21 (633.5)</td>
<td>5.79 \times 10^{-79}</td>
</tr>
<tr>
<td>Nervous, Tense</td>
<td>0.08</td>
<td>0.74</td>
<td>0.86</td>
<td>-2.88 (633.5)</td>
<td>7.52 \times 10^{-3}</td>
</tr>
<tr>
<td>Fearful, Anxious</td>
<td>0.08</td>
<td>0.68</td>
<td>1.05</td>
<td>-8.55 (633.5)</td>
<td>3.50 \times 10^{-17}</td>
</tr>
<tr>
<td>Feels Too Guilty</td>
<td>0.02</td>
<td>0.19</td>
<td>0.90</td>
<td>-23.63 (633.5)</td>
<td>1.49 \times 10^{-102}</td>
</tr>
<tr>
<td>Repeats Acts (Compulsion)</td>
<td>0.01</td>
<td>0.79</td>
<td>0.15</td>
<td>16.93 (633.5)</td>
<td>3.84 \times 10^{-56}</td>
</tr>
<tr>
<td>Strange Behavior</td>
<td>0.00</td>
<td>0.36</td>
<td>0.06</td>
<td>9.79 (633.5)</td>
<td>6.93 \times 10^{-23}</td>
</tr>
<tr>
<td>Strange Ideas</td>
<td>0.02</td>
<td>0.44</td>
<td>0.12</td>
<td>10.30 (633.5)</td>
<td>5.98 \times 10^{-24}</td>
</tr>
<tr>
<td>Worries</td>
<td>0.18</td>
<td>0.82</td>
<td>1.51</td>
<td>-16.55 (633.5)</td>
<td>8.04 \times 10^{-56}</td>
</tr>
<tr>
<td>Total OCS Scale Score</td>
<td>0.73</td>
<td>6.25</td>
<td>8</td>
<td>-10.04 (633.5)</td>
<td>7.03 \times 10^{-23}</td>
</tr>
</tbody>
</table>

The table shows the sex and age distribution as well as the mean of each OCS scale item score within each group, and the \( p \) value of the two-sample \( t \) test between G1 and G2. 

G, group; HC, healthy control; OCD, obsessive-compulsive disorder; OCS, Obsessive-Compulsive Symptom.
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For RSFC, abnormalities in G1 mainly occurred in the default mode network (dt), dorsal attention network (dla), ventral attention network (vta), and cingulo-opercular network (cgc). G1 showed decreased connectivity within the dla ($t_{3676} = -4.13, p = 3.74 \times 10^{-3}$), decreased connectivity between dla and dt ($t_{3676} = 3.96, p = 7.8 \times 10^{-5}$), FDR $q < .01$), and increased connectivity between vta and dt but increased FC among the dla, vta, and cgc compared with the HC group (FDR $q < .05$) (see Figure 3 and Table 3). G2 showed no significant FC differences compared with the HC group.

Associations Between Neuroimaging Differences and Psychiatric Symptoms and Cognitive Ability

We found that both gray matter volume and white matter FA reduced in G1 correlated negatively with the OCS scale and CBCL syndrome scales. For gray matter, the volumes of the bilateral precentral gyrus, IPL, and right precuneus correlated negatively with “cannot get mind off things (obsession)” (OCS scale), “repeated acts (compulsion)” (OCS scale), “strange behavior” (OCS scale), and a series externalized problems, while there were positive correlations with cognitive ability such as performance of oral reading recognition and list sorting working memory (Figure 4; Table S16 in Supplement 2).

Figure 2. Child Behavior Checklist (CBCL) syndrome scales and cognitive abilities in group 1 (G1) (red), group 2 (G2) (blue), and the healthy control (HC) group (gray). (A) Syndrome scales of the CBCL: anxious/depressed (anxdep), withdraw/depressed (withdep), somatic complaints (somatic), social problem (social), thought problems (thought), attentional problem (attention), rule-break behavior (rulebreak), aggressive problem (aggressive), internal problem (internal), external problem (external), total problems (totprob). Items from the CBCL DSM-Oriented Scales: depression disorder (depress), anxiety disorder (anxiety), somatic problems (somatic), attention-deficit/hyperactivity disorder (adhd), oppositional defiant problems (opposi), conduct problems (conduct). Items from the fourth edition of the CBCL (2007 revision): sluggish cognitive tempo (sct), obsessive-compulsive problems (ocd), stress problems (stress). (B) Cognitive abilities measured by the National Institutes of Health Toolbox Cognition Battery: picture vocabulary (picvocab), flanker inhibitory control (flanker), picture sequence memory (picture), card sort (cardsort), pattern comparison processing speed (pattern), oral reading recognition (reading), list sorting working memory (list), crystal intelligence (cryst), fluid computed intelligence (fluidcomp), total computed intelligence (totalcomp).

Figure 3. Multimodal neuroimaging differences between two obsessive-compulsive disorder subtypes (group 1 [G1] and group 2 [G2]) and healthy control (HC) subjects: (A) G1 vs. HC group; (B) G2 vs. HC group. * $p < .05$ (false discovery rate corrected). ** $p < .01$ (false discovery rate corrected). Significantly changed cortical regions, functional connections, and fiber bundles can be found in Tables S3–S6 in Supplement 2. Abbreviations of brain regions and white matter fibers can be found in Table 3. ad, auditory network; ATR, anterior thalamic radiations; ca, cinguloparietal network; cgc, cingulo-opercular network; CgC, cingulate cingulum; dla, dorsal attention network; dt, default mode network; Fmaj, forceps major; rob, frontal opercular network; Fmin, forceps minor; fo, frontal operculum; Fx, fornix; Fx.no Fim, fornix, excluding fimbria; L, left; n, none; pSLF, parietal superior longitudinal fasciculus; R, right; rl, retrolateral temporal network; sa, salience network; SIFC, striatal inferior frontal cortex tract; smh, sensorimotor hand network; smm, sensorimotor mouth network; tSLF, temporal superior longitudinal fasciculus (arcuate fasciculus); UNC, uncinate; vta, ventral attention network; vs, visual network.
For white matter, SCS FA correlated negatively with obsession and compulsion and with externalized problems, while it was positively associated with most cognitive abilities. RSFC was mainly related to social, thought, and attentional problems (Figure 4; Table S16 in Supplement 2).

**Potential Influence From Samples, Intelligence, ADHD Comorbidity, and Anxiety Disorder Comorbidity**

The main results were verified in the split-half cross-site-validation analyses. In the two halves of data, G1 showed a smaller volume of the right precentral gyrus, a smaller volume of the right IPL, lower SCS FA, a weaker connection within the dia (only in part 1), and a stronger connection between the dia and dt (only in part 1) (see Supplemental Results in Supplement 1).

For G1 vs. the HC group, the main results remained after regressing out intelligence as a covariate, except for intracranial volume difference (Tables S20–S22 in Supplement 2; Figure S11 in Supplement 1). These results suggest that intelligence may affect the difference at the level of whole brain volume but has little influence on the changes at local brain features.

We found a higher ADHD comorbidity rate in G1 ($n = 199$ of 909, 21.9%) than in G2 ($n = 29$ of 360, 8.1%), while a higher...
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Figure 4. Heatmap of correlation between the neuroimaging features (significantly changed in group 1 [G1] with false discovery rate $p < .01$) and behavioral/cognitive measures. The color bar represents the $t$ value of the regression coefficient from the mixed linear model. *False discovery rate $p < .05$, **false discovery rate $p < .01$, 07-occ, CBCL 2007 revision—obsessive-compulsive problems; 07-sct, CBCL 2007 revision—sluggish cognitive tempo; 07-stress, CBCL 2007 revision—stress problems; cardsort, card sort; CBCL, Child Behavior Checklist; cryt, crystal intelligence; CV, cortical volume; dia, dorsal attention network; dsm5-achd, CBCL DSM-Oriented Scale—attention-deficit/hyperactivity disorder; dsm5-anxdisord, CBCL DSM-Oriented Scale—anxiety disorder; dsm5-conduct, CBCL DSM-Oriented Scale—conduct problems; dsm5-depress, CBCL DSM-Oriented Scale—depression disorder; dsm5-oppoait; CBCL DSM-Oriented Scale—oppositional defiant disorder; DSM-Oriented Scale—somatic problems; dt, default mode network; FA, fractional anisotropy; FC, functional connectivity; flanker, flanker inhibitory control; fluidcomp, fluid computed intelligence; fSCS, frontal superior corticostriatal tract; IFOf, inferior frontal occipital fasciculus; ifpilh, left inferior parietal lobe; ifpirlh, right inferior parietal lobe; IFSC, inferior frontal to superior frontal cortical tract; ifmth, left inferior temporal lobe; ifmthl, right inferior temporal lobe; ILF, inferior longitudinal fasciculus; L, left; list, list sorting working memory; NIH, National Institutes of Health; OCS, Obsessive-Compulsive Symptom; pattern, pattern comparison processing speed; porh, right precuneus; picture, picture sequence memory; picvocab, picture vocabulary; precnllh, left precentral gyrus; precnrh, right precentral gyrus; pSCS, parietal superior corticostriatal tract; R, right; reading, oral reading recognition; SCS, superior corticostriatal tract; syn-aggressive, CBCL syndrome scale—aggressive problem; syn-anxdep, CBCL syndrome scale—anxious/depressed; syn-attention, CBCL syndrome scale—attentional problem; syn-external, CBCL syndrome scale—external problem; syn-internal, CBCL syndrome scale—internal problem; syn-rulebreak, CBCL syndrome scale—rule-break behavior; syn-social, CBCL syndrome scale—social problem; syn-somatic, CBCL syndrome scale—somatic complaints; syn-thought, CBCL syndrome scale—thought problems; syn-topprob, CBCL syndrome scale—total problems; syn-withdep, CBCL syndrome scale—withdraw/depressed; totalcomp, CBCL syndrome scale—total computed intelligence.

Anxiety disorder comorbidity rate was found in G2 ($n = 136$ of $360, 37.8\%$) than in G1 ($n = 182$ of $909, 20\%$). Subjects in G1 with ADHD showed a different pattern of impairments (Figure S4 in Supplement 1; Table S10 in Supplement 2). For intracranial volume, fiber tract FA, and RSFC, subjects with OCD with and without ADHD generally demonstrated significant alterations, similar to those of the whole G1 (Figure S4 in Supplement 1; Tables S11 and S12 in Supplement 2). After removing the patients with anxiety disorder, subjects in G2 still showed higher symptoms, especially in obsession, anxiety, and perfectionism, and a certain degree of impulsivity compared with the HC subjects (Table S23 in Supplement 2). In sum, these results suggest that our primary results were not driven by potential comorbidities.

**Longitudinal Analysis**

We found that the cognitive and mental symptom profiles of both subtypes of children with OCD-like symptoms remained relatively stable after 2 years of development, demonstrating the validity of our classification on an annual time scale (Figure S9 in Supplement 1). Longitudinal association analysis found that significantly altered brain features at baseline G1 were associated with crystallized intelligence and psychiatric symptoms (mainly compulsion and externalizing problems) 2 years later (Figure S10 in Supplement 1).

**DISCUSSION**

OCD is a heterogeneous disorder characterized by multiple symptom dimensions involving obsessions, compulsion, and anxiety, which may have distinct neural substrates. This study used multiple symptom domains and identified, for the first time, two subgroups with distinct symptom profiles, cognitive impairments, and neural differences in a large sample of children including those with obsessive-compulsive traits from the ABCD Study, which would help to resolve the heterogeneity of pediatric OCD and clarify the relationships between anxiety, compulsion, and perfectionism. Obsessive-compulsive personality traits have been identified as a possible risk factor for not only adult OCD, but also obsessive-compulsive personality disorder (53), the latter being characterized as extreme perfectionism, order, and neatness, often associated with anxiety, with a prevalence of 3% to 8% in adult populations (54).

By using clinical dimensional measures to establish categorical groups, our research combines the dimension-based and the category-based approaches to resolve heterogeneity (55–57). The difference between our clustering study and previous studies using the Yale-Brown Obsessive Compulsive Scale (58) is that we used the transdiagnostic dimensions, instead of specific compulsive action (such as sorting, cleaning, checking, harming, or hoarding) (22,23), which is more in line with the Research Domain Criteria (59,60) framework that considers OCD as a combination of defects in various neuro-psychological dimensions (61,62).

We found that only G1 (high level of compulsivity but less anxiety) showed 1) significant neuroanatomical alterations, including decreased volumes bilaterally of the precentral gyrus, IPL, and precuneus; 2) lower FA in white matter fiber tracts connecting the striatum with the frontal/parietal lobes; and 3) RSFC between the dt and dia. Findings 1 and 2 are broadly consistent with the results of Pagliaccio et al. (63) using the
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same ABCD Study data. By correlation analysis, they found that SCS FA and connectivity between the default mode network and dorsal attention network showed significant association with OCS scale scores. The difference between the results of Pagliaccio et al. and our study may arise from the different approach (correlation analysis vs. case-control study), modality (thickness vs. volume), and OCS scale score (clustering of OCS scale vs. factor analysis) used.

The significant volume reduction in the IPL and precuneus in G1 emphasizes the importance of parietal regions in OCD in addition to the classical cortico-striato-thalamo-cortical regions. Early studies using positron emission tomography in adult OCD patients showed reduced metabolic activity in this region (64,65). Recent studies have begun to show impairments of the IPL in OCD (11,66–68). For example, both pediatric and adult OCD patients showed thinner IPL in a large-scale, cross-site analysis (69,70). On the other hand, Menzies et al. (11) found that subjects adult OCD had increased gray matter in the parietal lobe, which was, however, positively related to their deficit in the stop signal task, indicating impaired inhibitory control. FA of white matter in the parietal regions was also shown to be reduced in subjects with OCD and their first-degree relatives (71). Moreover, de Wit et al. (72) and Morein-Zamir et al. (73) showed reduced activation of the right IPL during the stop signal reaction time task and reduced activation of the left IPL during attentional set shifting in OCD, respectively. The precuneus, which projects to prefrontal cortex densely and is associated with thought-action fusion (74), has been implicated as a key structure in OCD (75).

It should be noted that thalamic volume reduction was found in G1 [although this did not pass FDR correction, which is consistent with Pagliaccio et al. (63), who showed negative correlation between thalamic volume and symptom scores]. These results are inconsistent with the increased thalamic volume (12,76) found for OCD, possibly owing to different data collection, different analysis methods, and potential confounding factors such as age and other demographic features.

Some other externalizing symptoms commonly associated with ADHD tended to be clustered in G1, including conduct disorder and aggressive and oppositional deviant behavior. This is also consistent with dysfunctional cortico-striato-thalamo-cortical circuitry and the frontoparietal executive network, mediating attention and inhibitory control (77–79). Moreover, de Wit et al. (72) and Morein-Zamir et al. (73) found more evidence of lateral prefrontal cortex underactivity associated with stopping deficits in adult ADHD in comparison with the shifting impairments in adult OCD associated with parietal lobe underactivity. Note that Pagliaccio et al. reported that the factor analysis–based OCS scale score correlated positively with cognitive ability after controlling for the CBCL-ADHD scores (63), and they ascribed the cognitive impairments of OCD instead to ADHD. We also calculated this correlation but used each OCS item (partial correlations, with CBCL-ADHD score as a covariate). We found that anxiety (#45, #50, #52, #112) and perfectionism (#32) showed a positive correlation with cognitive scores (consistent with Pagliaccio et al.), while compulsion (#66) and strange behavior (#84) showed a negative correlation with cognitive abilities (Figure S9 in Supplement 1), suggesting that cognitive impairments in G1 are not due to ADHD but may be related to compulsivity. The positive correlation found by Pagliaccio et al. is more in line with our G2 with high anxiety, in which subjects showed superior cognition.

It is less clear precisely how the parietal deficits lead directly to the main symptoms of OCD. In particular, the IPL and precuneus (which have structural differences in G1) may contribute to several functional networks including the dt (subserving introspective cognitive processes), the dia, and frontoparietal network (subserving external-directed attentional tasks) (80,81). In this study, we also found increased RSFC between the default mode network and dorsal attention network, consistent with the elevated connectivity between the dt and frontoparietal networks in OCD (13), perhaps related to a disturbance between internalizing and externalizing task performance (13,82). These neural differences associated with the parietal lobe in G1 were all more correlated with compulsivity and externalizing problems than with anxiety and internalized symptoms (see Figure 4; Figure S4 in Supplement 1). In another transdiagnostic analysis of 12 psychiatric and neurological disorders, the areas most affected were concentrated in the parietal lobe, including the precentral gyrus and IPL (83). This implies that the dysfunctional parietal lobe is associated with a general psychiatric risk, which is already evident in children as young as 10 years of age.

In addition to parietal gray matter volume reduction, we also observed significant and extensive reduction of white matter fiber FA in G1 (mainly connecting the frontal and parietal lobes with the striatum), which correlated negatively with obsessions, repeated acts, and strange behavior. These results are in line with the current neurobiological models of OCD that propose abnormalities in corticostriatal circuits (84). Corticostriatal projections play an essential role in the balance between the so-called goal-directed and habitual control systems (85,86), which, if disrupted, may prevent flexible and effective decision making and lead to OCD and other disorders of compulsivity (10,19,87,88). Recently, in a large sample of healthy adolescents, compulsivity has been shown to be predicted by a relative slowing in development of model-based (i.e., goal-directed) behavior and reduced frontostriatal connectivity (89). Moreover, the precentral gyrus, that part of the motor cortex immediately adjacent to the premotor cortex, had significantly reduced volume in G1 that correlated negatively with the increased incidence of repeated acts. Impairments in this structure may similarly be related to abnormalities of control of habits (10,90,91) and its relationship with goal-directed behavior (92).

The significant neural differences in frontoparietal regions and corticostriatal projections in G1, accompanied by higher compulsivity and obsession, lower anxiety, and extensive cognitive impairments, contrast sharply with the defining features of G2, i.e., higher anxiety, lower compulsivity and obsessions, absence of cognitive impairment, and less evidence of neural deficits. The dissociation between anxiety on the one hand and compulsions on the other raises the important question regarding the interrelationship between obsession (including perfectionism), compulsion, and anxiety in OCD (19,92,93). The present findings for G1 are consistent with the classic view of anxiety reduction motivating compulsions only
if it is assumed that repeated acts indeed successfully reduce anxiety. However, the lack of correlation is also consistent with observations that anxiety is often not the critical trigger of compulsive or ritualistic behavior in childhood (94). In contrast, as for subjects in G2 in this study, high levels of anxiety are often reported to be associated with perfectionist tendencies (as measured by parent report) (95,96), the behavioral aspects of which presumably do not lead to anxiety reduction. More longitudinal studies would be required to resolve precise issues of causality.

The two distinct OCD-like subtypes suggest different therapeutic approaches. Currently, the selective serotonin reuptake inhibitors are the mainstay of the pharmacological treatment of OCD. Considering that selective serotonin reuptake inhibitors are also effective for anxiety disorders (97,98), patients with subtype G2 may benefit from selective serotonin reuptake inhibitors for treating their high levels of anxiety. In comparison, there is a high priority to develop new, effective early interventions for subtype G1, considering the presence of higher compulsivity, lower anxiety, and significant structural and functional differences. For example, an appropriately tailored cognitive behavioral therapy may be developed, possibly combined with medication.

Limitations
The study has several limitations. First, we used consensus hierarchical clustering with the optimal number of clusters determined by combining multiple factors, which is not definitive. We have validated the results using nonhierarchical clustering methods and split-half cross-site validation. Second, we used the CBCL OCS scale (parent report), which may not be as definitive as psychiatric diagnoses such as in the DSM-5 and may not be optimal for the report of subjective symptoms such as anxiety. However, the OCS scales has been demonstrated to show good psychometric properties, show high prevalence, and be related to familial/parental factors (63). Moreover, the OCS scale covers multiple psychometric domains such as anxiety, obsessions, and compulsivity, which allows deeper investigations of their interrelationships. Third, the OCD population has comorbidities. However, we have shown that comorbidity within subgroup G1 (high compulsivity with low anxiety) does not drive the neuroimaging differences identified; thus, the influence of comorbidities may be limited. Finally, this is a cross-sectional study using only a U.S. population, and future, more cross-national and cross-racial data are required to verify the current findings.

ACKNOWLEDGMENTS AND DISCLOSURES
This work was supported by the Shanghai Municipal Science and Technology Major Project (Grant No. 2018SHZDZX01 [to JZ], the ZJ Lab (to JZ), the Shanghai Center for Brain Science and Brain-Inspired Technology (NSFC Grant No. 61973086 [to JZ]), the 111 Project (Grant No. B18015 [to JF]), the key project of Shanghai Science and Technology (Grant No. 16JC1420402 [to JF]), the National Key R&D Program of China (Grant No. 2018YFC1312900 [to JF]), the National Natural Science Foundation of China (NSFC Grant No. 91630314 [to JF]). Data used in this article were from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org). The ABCD Study is supported by the National Institutes of Health and additional federal partners (Grant Nos. U01DA0411156, U01DA041714, U24DA041123, U24DA041147, U01DA041093, and U01DA041025). This article reflects the opinions of the authors and might not reflect the opinions of the National Institutes of Health or ABCD Consortium investigators. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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