Structural and Functional Brain Abnormalities in Attention-Deficit/Hyperactivity Disorder and Obsessive-Compulsive Disorder: A Comparative Meta-analysis

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**IMPORTANCE**
Patients with attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) share impaired inhibitory control. However, it is unknown whether impairments are mediated by shared or disorder-specific neurostructural and neurofunctional abnormalities.

**OBJECTIVE**
To establish shared and disorder-specific structural, functional, and overlapping multimodal abnormalities in these 2 disorders through a voxel-based meta-analytic comparison of whole-brain gray matter volume (GMV) and functional magnetic resonance imaging (fMRI) studies of inhibition in patients with ADHD and OCD.

**DATA SOURCES**

**STUDY SELECTION**
Whole-brain voxel-based morphometry (VBM) or fMRI studies during inhibitory control comparing children and adults with ADHD or OCD with controls.

**DATA EXTRACTION AND SYNTHESIS**
Voxel-wise meta-analyses of GMV or fMRI differences were performed using Seed-based d-Mapping. Regional structure and function abnormalities were assessed within each patient group and then a quantitative comparison was performed of abnormalities (relative to controls) between ADHD and OCD.

**MAIN OUTCOMES AND MEASURES**
Meta-analytic disorder-specific and shared abnormalities in GMV, in inhibitory fMRI, and in multimodal functional and structural measures.

**RESULTS**
The search revealed 27 ADHD VBM data sets (including 931 patients with ADHD and 822 controls), 30 OCD VBM data sets (928 patients with OCD and 942 controls), 33 ADHD fMRI data sets (541 patients with ADHD and 620 controls), and 18 OCD fMRI data sets (287 patients with OCD and 284 controls). Patients with ADHD showed disorder-contrastings multimodal structural (left $z = 1.904, P < .001$; right $z = 1.738, P < .001$) and functional (left $z = 1.447, P < .001$; right $z = 1.229, P < .001$) abnormalities in bilateral basal ganglia/insula, which were decreased in GMV and function in patients with ADHD relative to those with OCD (and controls). In OCD patients, they were enhanced relative to controls. Patients with OCD showed disorder-specific reduced function and structure in rostral and dorsal anterior cingulate/medial prefrontal cortex (fMRI $z = 2.113, P < .001$; VBM $z = 1.622, P < .001$), whereas patients with ADHD showed disorder-specific underactivation predominantly in the right ventrolateral prefrontal cortex ($z = 1.229, P < .001$). Ventromedial prefrontal GMV reduction was shared in both disorders relative to controls.

**CONCLUSIONS AND RELEVANCE**
Shared impairments in inhibitory control, rather than representing a transdiagnostic endophenotype in ADHD and OCD, were associated with disorder-differential functional and structural abnormalities. Patients with ADHD showed smaller and underfunctioning ventrolateral prefrontal/insular-striatal regions whereas patients with OCD showed larger and hyperfunctioning insular-striatal regions that may be poorly controlled by smaller and underfunctioning rostro/dorsal medial prefrontal regions.

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Attention-deficit/hyperactivity disorder (ADHD) is defined as age-inappropriate problems with inattention, impulsivity, and hyperactivity and affects 5% to 8% of children and 4% of adults worldwide.  

Obsessive-compulsive disorder (OCD) has a prevalence of approximately 1% to 2% and is defined by obsessions, that is, recurrent and intrusive thoughts (eg, about contamination, harm, or symmetry) and compulsions, that is, repetitive, ego-dystonic and time-consuming behavioral and mental rituals (eg, repetitive washing or checking).  

Attention-deficit/hyperactivity disorder and OCD frequently co-occur in clinical and epidemiological samples with shared familiarity and heritability.  

Both disorders have deficits in inhibitory control, thought to underlie impulsivity in ADHD and poor control over obsessions and compulsions in OCD. Inhibitory control refers to the ability to inhibit goal-irrelevant behaviors and cognitions and is measured in tasks of response and interference inhibition, or switching. Response inhibition tasks require the inhibition to no-go stimuli among prepotent go stimuli (go/no-go task) or the withdrawal of already triggered motor responses after stop signals (stop task). Interference inhibition tasks require the overriding of a prepotent response that interferes with the instructed action.  

Switching paradigms require inhibition of previously valid stimulus-response associations and response to new ones. Neuroimaging studies show overlapping inhibitory control networks centered on the ventrolateral prefrontal cortex (VLPFC), anterior insula (AI), supplementary motor area (SMA), dorsal anterior cingulate cortex (dACC), and the striatal, thalamic, and inferior parietal regions.  

In ADHD, meta-analyses of functional magnetic resonance imaging (fMRI) studies of response and interference inhibition report consistent underactivation relative to controls in the right and left VLPFC/AI, SMA, and caudate while switching also elicits reduced activation in bilateral VLPFC/AI and basal ganglia.  

Moreover, poor inhibition performance correlates with decreased gray matter volumes (GMVs) in the VLPFC, AI, anterior cingulate cortex (ACC), striatal, and temporoparietal regions. A meta-analysis of region of interest (ROI) studies found reduced GMV in the prefrontal, striatal, parietal, and cerebellar regions.  

Whereas meta-analyses of voxel-based morphometry (VBM) studies report consistent GMV reductions in the basal ganglia.  

In OCD, fMRI studies of inhibitory control reported altered striatal activation and decreased activation in rostral and dorsal ACC and medial prefrontal cortex (r/d ACC/MPCF).  

Meta/mega-analyses of whole-brain VBM studies in OCD have found decreased GMV in r/d ACC/MPCF and ventromedial orbitofrontal cortex (vmOFC), and increased GMV in bilateral striatum, which furthermore was associated with poor inhibition performance.  

Shared deficits in frontostriatal-mediated inhibitory control in ADHD and OCD may suggest a shared transdiagnostic phenotype. However, it remains unknown whether this phenotype is mediated by shared or distinct neural underpinnings because no structural MRI studies and only 3 fMRI studies have directly compared the disorders. The fMRI studies found disorder-specific underactivation in ADHD relative to OCD in the right VLPFC during switch and stop tasks, and in basal ganglia during switch and oddball tasks.  

However, these studies were based on small numbers and hence underpowered.  

The study aim was therefore to conduct a quantitative, voxel-based meta-analytic comparison of all published whole-brain structural MRI studies of GMV abnormalities and all whole-brain fMRI studies of inhibition in children and adults with ADHD and OCD to establish shared and disorder-specific structural and functional abnormalities, as well as multimodal structural and functional abnormalities, by conducting conjunction/disjunction analyses across VBM and fMRI studies.  

For the VBM meta-analysis, we hypothesized that patients with OCD would show disorder-specific GMV decrease in the r/d ACC/MPCF whereas we expected disorder-contrasting GMV abnormalities in the basal ganglia, with decreased volumes in ADHD and increased volumes in OCD relative to controls and each other. For the inhibition fMRI meta-analysis, we hypothesized that both patient groups would show altered striatal activation (References 18, 19, 21–23, 25, 26, 33–41, 51) but that patients with ADHD would demonstrate disorder-specific underactivation in the VLPFC, whereas patients with OCD would demonstrate disorder-specific underactivation in the r/d ACC/MPCF.  

Methods  

Search and Inclusion of Studies  

A comprehensive literature search was performed using the PubMed, ScienceDirect, Web of Knowledge, and Scopus research databases through September 30, 2015 (see eMethods, eResults, and eReferences in the Supplement). In addition, manual searches were conducted among the reference databases.
sections of retrieved studies and review articles. Included studies provided whole-brain pairwise voxel-based comparisons of adult and pediatric patient groups (OCD or ADHD) relative to controls using VBM or fMRI. For fMRI, only inhibitory control tasks were included (ie, stop, go/no-go, Stroop, Simon, Eriksen flanker, multisource interference, or task-switching paradigms). Included contrasts compared inhibitory control (ie, stop, no-go, incongruent, or switch trials) against a control condition (ie, failed stop, go, oddball, congruent, or repeated trials). Studies were excluded if they had fewer than 10 patients, no case-control comparisons, used only ROI analyses, or had duplicated patient data.18,19,31,44,45 A minimum of 10 participants is a commonly used compromise threshold for study inclusion in meta-analyses because studies with smaller sample sizes are underpowered and would bias the meta-analysis downward.31,32,44,54-56 Only whole-brain data sets were included in order to remove bias inherent in ROI analyses.57 Additional details (peak coordinates or statistical maps) were obtained from authors wherever necessary. L.I.N., S.L., and C.C. assessed all articles and achieved 100% agreement.

Meta-analysis

Voxel-wise meta-analyses of regional brain differences were conducted using the anisotropic effect-size version of the Seed-based d Mapping (AES-SDM) software package (http://www.sdmproject.com),19,49,50 following MOOSE guidelines for meta-analyses of observational studies.58 AES-SDM uses an anisotropic nonnormalized Gaussian kernel to recreate an effect-size map and an effect-size variance map for the contrast between patients and controls from peak coordinates and effect sizes for each individual VBM or fMRI study. Following this, a mean map is created by performing a voxel-wise calculation of the random-effects mean of the study maps, weighted by sample size and variance of each study and between-study heterogeneity. Statistical significance was determined using standard randomization tests.

First, separate analyses were performed examining regional GMV and activation abnormalities within each patient group relative to controls. Following this, a quantitative comparison was performed of abnormalities (relative to controls) in GMV and functional activation between ADHD and OCD by calculating the difference between each patient group in each voxel, and then using standard randomization tests to establish statistical significance.45 To examine medication effects, meta-regression analyses were performed within each patient group and for each imaging modality examining the effects of the percentage of participants who received treatment with either stimulants (ADHD) or antidepressants (OCD) on structural and functional abnormalities relative to controls.54,49

A conjunction/disjunction analysis was then conducted to examine areas of shared/contrasting abnormalities across both patient groups relative to controls, by computing the union of the P values for each patient group within each voxel while accounting for noise in the estimation of meta-analytic P values.49 This conjunction method was also used within patient groups to perform multimodal analyses, which show regions of overlapping functional and structural abnormalities relative to controls. Finally, a conjunction/disjunction analysis was performed using the patient group comparison maps to elucidate regions that were shared/differed between patient groups across both modalities.

Some studies used multiple task contrasts, several functional tasks, or identical controls. Combined maps with reduced variance were calculated to avoid dependent data in the analyses (see eMethods in the Supplement).

The inclusion of several different paradigms to assess inhibitory control introduces some task-related heterogeneity. However, because there were not sufficient studies to conduct subgroup analyses by task type, a supplementary meta-analysis was performed covarying for task type (response or interference inhibition, switching tasks).

For the meta-analyses, a statistical threshold of P < .005 was used with a cluster extent of 20 voxels. For the meta-regressions, a threshold of P < .0005 was used, with only regions found in the main analysis being included.44,49 Jack-knife sensitivity analyses were performed to assess robustness of findings; each analysis was repeated excluding 1 data set at a time to establish whether each cluster remained significant. For each significant cluster for patient-control comparison, the Egger test was used to assess the asymmetry of funnel plots to examine potential publication bias.59

Results

Included Studies and Sample Characteristics

A total of 2303 records were identified. After duplicates were removed, 1081 records were screened and 180 full-text articles were assessed for eligibility. Of these, 97 articles were included in the final meta-analysis (eFigure 1 in the Supplement). The search revealed 27 ADHD VBM data sets (including 931 patients with ADHD and 822 controls), 30 OCD VBM data sets (928 patients with OCD and 942 controls), 33 ADHD fMRI data sets (541 patients with ADHD and 620 controls), and 18 OCD fMRI data sets (287 patients with OCD and 284 controls) (Tables I-4 in the Supplement).

In the VBM analysis, sample size-weighted t tests revealed that patient groups did not differ in age (t55 = 1.93; P = .06), but ADHD studies contained a significantly greater proportion of males (t55 = 3.08; P = .003). Too few VBM studies included IQ scores to include them in the meta-analyses.

In the fMRI meta-analysis, a larger proportion of patients with ADHD were males (t49 = 3.18; P = .003) and were younger (t49 = 2.77; P = .008), but there was no significant difference from patients with OCD on IQ (t49 = 1.41; P = .17) (Table 1). Age and sex were consequently included as covariates in all between-group meta-analyses and a subgroup meta-analysis was performed including only the adult studies, which were age and sex matched.

Furthermore, to take account of potential developmental effects, a pediatric VBM subgroup meta-analysis was performed (eTable 5 in the Supplement). Too few (only 4 distinct pediatric OCD samples) OCD fMRI data sets were available to allow for an fMRI pediatric subgroup meta-analysis.
Table 1. Demographic Information for Studies Included in Meta-Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADHD</th>
<th>OCD</th>
<th>ADHD Controls</th>
<th>OCD Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>931</td>
<td>928</td>
<td>822</td>
<td>942</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>621 (66.7)</td>
<td>481 (51.8)</td>
<td>557 (67.8)</td>
<td>492 (52.2)</td>
</tr>
<tr>
<td>Mean (range) age, y*</td>
<td>22.9 (6-59)</td>
<td>27.9 (8-63)</td>
<td>22.8 (6-59)</td>
<td>27.5 (9-60)</td>
</tr>
<tr>
<td>Mean IQ (range)</td>
<td>104.4 (88.0-116.0)</td>
<td>108.5 (102.0-114.4)</td>
<td>109.8 (91.9-125.0)</td>
<td>113.8 (108.0-117.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder.

* Differences in age and IQ were tested using sample-size–weighted t tests. Corresponding sample-size–weighted means are presented.

Voxel-Based Morphometry

Global GMV did not differ between patients with ADHD and controls (d = 0.059, z = 0.396; P = .69), between patients with OCD and controls (d = 0.089, z = 0.830; P = .41), or between patient groups (d = 0.147, z = 0.589; P = .56).

Regional Differences in GMV

ADHD VBM

Patients with ADHD showed decreased GMV relative to controls in the right basal ganglia/anterior/posterior insula, vmOFC/MPFC/rACC, and left occipital lobe (Table 2 and Figure, A). The meta-regression analysis showed no association between any of these GMV abnormalities and long-term stimulant medication use.

OCD VBM

Patients with OCD relative to controls showed significantly decreased GMV in a large cluster comprising r/dACC/MPFC, vmOFC, in bilateral dorso-lateral prefrontal cortex (DLPFC) extending into the right premotor cortex, in the left VLPFC/premotor cortex/superior temporal lobe (STL), and the right angular gyrus. Significantly increased GMV was present in the bilateral putamen/nucleus accumbens/pallidium/amygdala/insula extending into the left caudate nucleus, and in bilateral cerebellum (Table 2 and Figure, A). The meta-regression analysis showed no association between GMV abnormalities and antidepressant treatment.

VBM Comparison in ADHD and OCD

Covarying for age and sex, disorder-specific reduced GMV was observed in patients with ADHD vs OCD in bilateral basal ganglia/amygdala/anterior/posterior insula, left occipital lobe, and vmOFC. Patients with OCD had decreased GMV relative to those with ADHD in the r/dACC/MPFC, vmOFC/vACC, left VLPFC/STL, and right DLPFC/VLPFC/premotor cortex (Table 2 and Figure, A).

The conjunction/disjunction analysis revealed that the right putamen/insula GMV abnormality (Montreal Neurological Institute [MNI] coordinates, 30, −12, 4; 248 voxels) was disjunctive, that is, decreased in ADHD but enlarged in OCD relative to HCs, while decreased vmOFC GMV was shared between disorders (MNI coordinates, 0, 42, −14; 126 voxels) (Figure, A).

The pediatric subgroup meta-analysis showed that the disjunctive VBM posterior insula/putamen cluster (MNI coordinates, 34, −4, 4; 271 voxels) remained (decreased in ADHD, increased in OCD). Patients with OCD also had reduced GMV in bilateral VLPFC/DLPFC (eTables 5-7 and eFigure 2 in the Supplement).

Differences in Inhibitory Brain Activation

fMRI in ADHD

Patients with ADHD relative to controls showed underactivation in bilateral VLPFC/insula/STL/putamen, right caudate nucleus, and SMA (Table 3 and Figure, B). No overactivation was observed. Long-term stimulant medication use was associated with increased activation in the left VLPFC/insula/STL (MNI coordinates, −48, 8, 0; z = 1.6; P < .001; 401 voxels) (eFigure 3 in the Supplement), right VLPFC/insula (MNI coordinates, 42, 20, 0; z = 1.5; P < .001; 114 voxels) (Figure 4 in the Supplement), right MTL/STL (MNI coordinates, 58, −16, −10; z = 1.4; P < .001; 229 voxels) (eFigure 5 in the Supplement); and decreased SMA activation (MNI coordinates, −4, 6, 48; z = 1.6; P < .001; 56 voxels) (eFigure 6 in the Supplement).

fMRI in OCD

Relative to controls, patients with OCD showed underactivation in the r/dACC/MPFC, right caudate nucleus, cerebellum, STL/occipital lobe, and left postcentral gyrus. Increased activation was found in the left posterior insula/putamen/VLPFC/premotor/postcentral/STL and right premotor cortex (Table 3 and Figure, B). The meta-regression analysis showed no association between fMRI abnormalities and antidepressant treatment.

fMRI Comparing ADHD vs OCD

Attention-deficit/hyperactivity disorder was associated with disorder-specific underactivation relative to OCD in bilateral VLPFC/Al/putamen, reaching into the premotor cortex, posterior insula, and left STL. Obsessive-compulsive disorder was associated with disorder-specific underactivation in the r/dACC/MPFC, right occipital lobe, amygdala and cerebellum, and left postcentral/premotor cortex relative to ADHD (Table 3 and Figure, B). The conjunction/disjunction analysis showed no shared or disjunctive functional abnormalities.

Subgroup and Supplementary Meta-analyses

After controlling for task type, the majority of between-patient findings remained except the underactivation in patients with OCD in the right amygdala, right occipital lobe, and...
left postcentral/premotor cortex. After taking into account overlaps in patients and controls across multiple functional tasks, group differences in the right amygdala were no longer significant and the peak height of the right VLPFC/AI/putamen cluster was reduced ($z = 0.878; P < .001; 221$ voxels). All other between-group clusters remained. All main disorder-specific findings were robust as shown in jackknife analyses (see eTables 8-13 in the Supplement). Results were also largely replicated in the age- and sex-matched adult subgroup meta-analysis (see eTables 14-16 and eFigure 7 in the Supplement).

**Multimodal VBM and fMRI Analyses**

**Multimodal Analysis in ADHD**

One overlapping cluster in the right putamen/AI showed both decreased GMV and reduced activation in patients with ADHD relative to controls (MNI coordinates, $24, 0, 8; 153$ voxels) (Figure, C).

**Multimodal Analysis in OCD**

In patients with OCD, decreased GMV and functional activation relative to controls overlapped in the r/dACC/dMPFC (MNI coordinates, $-2, 28, 38; 1356$ voxels) while increased GMV overlapped with increased activation in the left putamen and posterior insula (MNI coordinates, $-32, -8, 0; 215$ voxels). The left premotor cortex was decreased in volume and increased in activation in patients with OCD relative to those with ADHD. Smaller structure and decreased

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**Table 2. Meta-analysis Results for Voxel-Based Morphometry Studies in Attention-Deficit/Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD)**

<table>
<thead>
<tr>
<th>Contrast</th>
<th>MNI Coordinates</th>
<th>SDM $z$ Score</th>
<th>P Value</th>
<th>Voxels, No.</th>
<th>Brodmann Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD Decreased vs Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right putamen/pallidum/insula</td>
<td>$24, -8, 7$</td>
<td>$2.303$</td>
<td>$&lt;.001$</td>
<td>$1550$</td>
<td>$13$</td>
</tr>
<tr>
<td>vmOFC/vMPFC/rACC</td>
<td>$2, 41, -21$</td>
<td>$2.270$</td>
<td>$&lt;.001$</td>
<td>$1350$</td>
<td>$11, 10, 9, 32$</td>
</tr>
<tr>
<td>Right caudate nucleus</td>
<td>$18, 8, 14$</td>
<td>$2.154$</td>
<td>$&lt;.001$</td>
<td>$370$</td>
<td></td>
</tr>
<tr>
<td>Left occipital lobe</td>
<td>$-10, -94, 14$</td>
<td>$1.768$</td>
<td>$&lt;.001$</td>
<td>$336$</td>
<td>$17, 18$</td>
</tr>
</tbody>
</table>

| OCD vs Control                       |                 |               |         |             |                |
| OCD increased vs control             |                 |               |         |             |                |
| Left putamen/caudate/nucleus         | $-28, 4, 2$     | $2.588$       | $<.001$ | $1482$      | $13$           |
| Right putamen/nucleus/acumbens/pallidum/amygdala/insula | $24, 4, -2$   | $2.089$       | $<.001$ | $928$       | $13$           |
| Left cerebellum                      | $-14, -40, -21$ | $1.349$       | $<.001$ | $196$       |                |
| Right cerebellum                     | $23, -37, -24$  | $1.224$       | $<.005$ | $12$        |                |
| OCD decreased vs control             |                 |               |         |             |                |
| r/dACC/MPFC/vmOFC                    | $-2, 28, 36$    | $2.693$       | $<.001$ | $3299$      | $32, 24, 8, 9, 10, 11$ |
| Left VLPC/premotor/STL               | $-52, 18, 12$   | $2.315$       | $<.001$ | $997$       | $44, 45, 46, 9, 43, 22$ |
| Right angular gyrus                  | $52, -56, 38$   | $1.718$       | $<.001$ | $274$       | $39, 40$       |
| Right DLPFC/premotor cortex          | $42, 12, 32$    | $1.589$       | $<.005$ | $80$        | $9, 6$         |
| Left DLPFC                           | $-28, 34, 38$   | $1.610$       | $<.005$ | $54$        | $9$            |

| ADHD (vs Control) vs OCD (vs Control) |                 |               |         |             |                |
| ADHD (vs control) decreased vs OCD (vs control) | $-28, 4, -2$ | $1.904$       | $<.001$ | $1333$      | $13$           |
| Right putamen/acumbens/pallidum/insula | $24, 4, -2$   | $1.738$       | $<.001$ | $841$       | $13$           |
| Left occipital lobe                  | $-10, -94, 12$  | $1.342$       | $<.001$ | $294$       | $17, 18$       |
| Right caudate nucleus                | $14, 16, 4$     | $1.323$       | $<.001$ | $65$        |                |
| vmOFC                               | $-4, 56, -26$   | $1.297$       | $<.001$ | $51$        | $11$           |

| OCD (vs control) decreased vs ADHD (vs control) |                 |               |         |             |                |
| r/dACC/MPFC                           | $2, 28, 28$     | $1.622$       | $<.001$ | $1425$      | $32, 24, 8, 9$ |
| Left VLPC/STL                         | $-52, 14, 10$   | $1.383$       | $<.001$ | $925$       | $44, 45, 9, 22$ |
| Right DLPFC/premotor cortex           | $44, 12, 32$    | $1.052$       | $<.001$ | $120$       | $9, 6$         |
| vmOFC/vACC                            | $6, 32, -10$    | $1.154$       | $<.001$ | $114$       | $11, 24, 32$   |

Abbreviations: dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; dMPFC, dorsomedial prefrontal cortex; MTL, middle temporal lobe; MNI, Montreal Neurological Institute; rACC, rostral anterior cingulate; rMPFC, rostromedial prefrontal cortex; STL, superior temporal lobe; vACC, ventral anterior cingulate cortex; VLPC, ventrolateral prefrontal cortex; vmOFC, ventromedial orbitofrontal cortex; vmPFC, ventromedial prefrontal cortex.

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**Multimodal Comparison in ADHD and OCD**

The multimodal comparison showed that the dACC/dMPFC was disorder-specifically decreased in both GMV and inhibitory activation in patients with OCD compared with those with ADHD (MNI coordinates, $-2, 28, 30; 929$ voxels). Enlarged structure and increased function in the left putamen/insula (MNI coordinates, $-30, -8, 4; 330$ voxels) was found in patients with OCD relative to those with ADHD. Smaller structure and decreased
function in the right putamen/AI (MNI coordinates, 28, 18, 0; 58 voxels) were disorder specific in patients with ADHD relative to those with OCD, who showed enlarged GMV relative to controls and patients with ADHD (Figure, O).

Publication Bias
The results of the Egger tests were nonsignificant (P > .05 for all comparisons, Bonferroni corrected), suggesting that there was no publication bias.

Discussion
The meta-analytic comparison showed that patients with ADHD and OCD have predominantly disorder-specific patterns of structural and inhibitory functional abnormalities. Patients with ADHD and OCD showed disorder-contrasting structural and functional abnormalities in the basal ganglia and insula that were reduced in GMV in patients with ADHD relative to controls and those with OCD, in whom they were increased relative to controls. Furthermore, structurally and functionally overlapping regions in bilateral putamen and the right anterior and left posterior insula were both reduced in GMV and in activation in the ADHD group relative to the OCD group, where they were increased relative to controls. In the stringent VBM disjunction analysis, the right anterior and posterior insula and putamen GMV in particular were disorder contrasting, as they were decreased in patients with ADHD but increased in those with OCD relative to each other and controls. In prefrontal regions, patients with OCD showed disorder-specific reduced overlapping function, as well as structure, in r/dACC/MPFC, whereas patients with ADHD showed disorder-specific inhibitory underactivation predominantly in the right VLPFC. Shared structural abnormalities were observed in vmOFC.

Both the contrasting GMV and functional abnormalities in bilateral basal ganglia and insula in ADHD and OCD extend previous meta-analytic findings in the individual patient groups of reduced GMV and function in basal ganglia/insula in ADHD and OCD and increased volumes and abnormal function in OCD. They also reinforce that abnormal GMV in the basal ganglia is related to abnormal inhibitory function, extending previous findings that poorer inhibitory control is associated with enlarged basal ganglia GMV in OCD but with decreased basal ganglia GMV in ADHD. The basal ganglia and insula are key components of salience detection, motiva-

Figure. Results of Voxel-Based Morphometry (VBM) and Functional Magnetic Resonance Imaging (fMRI) Meta-analyses for Each Disorder and the Comparison Between Disorders

A, Results of VBM meta-analysis for, from top to bottom, patients with attention-deficit/hyperactivity disorder (ADHD) relative to controls, patients with obsessive-compulsive disorder (OCD) relative to controls, the comparison between ADHD (vs controls) and OCD (vs controls), and conjunction/disjunction analysis of ADHD and OCD abnormalities (vs controls). The vmOFC GMV deficit is shared between disorders, while the insula/putamen GMV deficit is dissociated between disorders, that is, larger in OCD and smaller in ADHD. B, Results of fMRI meta-analysis for, from top to bottom, patients with ADHD relative to controls, patients with OCD relative to controls, and the comparison between OCD (vs controls) and ADHD (vs controls). C, Multimodal fMRI-VBM conjunction/disjunction analysis for, from top to bottom, overlapping deficits in patients with ADHD relative to controls, overlapping deficits in patients with OCD relative to controls, and the comparison between patients with OCD (vs controls) and patients with ADHD (vs controls). Green indicates increased in patients with OCD vs controls. Warm colors (yellow in ADHD, red in OCD) indicate decreased in patients vs controls. Orange indicates shared decreases in patients relative to controls. Purple indicates regions that were disjunctive across modalities (ie, increased in one but decreased in the other) in ADHD compared with OCD (vs controls).
tion, and habit-learning networks,\textsuperscript{10,60-64} which are modulated by dopaminergic activity,\textsuperscript{60,61,63,64} which is typically decreased in ADHD\textsuperscript{63,65,66} and increased in OCD.\textsuperscript{67,68} Consequently, the benchmark treatment for ADHD involves stimulant medications that increase striatal dopamine activity\textsuperscript{63} and enhance right inferior frontal, AI, and putamen activation,\textsuperscript{69} whereas dopamine antagonists are effective augmentation medications in OCD.\textsuperscript{70} There is consistent evidence for abnormal salience-processing networks in ADHD\textsuperscript{39,51,71-74} and OCD.\textsuperscript{39} We have previously found differential insula and striatum activation between patients with ADHD and those with OCD during salience processing, with enhanced activation in OCD and reduced activation in ADHD, which further correlated inversely with patients’ respective symptom severity.\textsuperscript{39} The finding of enlarged structure and function in the basal ganglia and insula in OCD may be a neuroplastic consequence of increased insula-striatal activation during symptom provocation,\textsuperscript{75,76} which may mediate habit-like compulsions and misattributions of emotional and behavioral salience to symptom-provoking stimuli.\textsuperscript{61,76} Enhanced bottom-up influence of the basal ganglia and insula in OCD may represent increased automatic or habitual responding at the expense of goal-driven behavior.\textsuperscript{5,61} In ADHD, deficient striato-insular activation may result in reduced task-related salience detection and task engagement, resulting in increased distractibility.\textsuperscript{39,43,71-74}

<table>
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<tr>
<th>Contrast</th>
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<th>SDM z Score</th>
<th>P Value</th>
<th>Voxels, No.</th>
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Abbreviations: dACC, dorsal anterior cingulate cortex; dMPFC, dorsomedial prefrontal cortex; HMTL, middle temporal lobe; MNI, Montreal Neurological Institute; rACC, rostral anterior cingulate cortex; rMPFC, rostromedial prefrontal cortex; SMA, supplementary motor area; STL, superior temporal lobe; vACC, ventral anterior cingulate cortex; vmOFC, ventromedial orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex.
be disorder-specifically underactivated in ADHD relative to conduct disorder\textsuperscript{24,53,74,77} and bipolar disorder\textsuperscript{78,79} suggesting that VLPFC underactivation may be a disorder-specific neurofunctional biomarker for ADHD relative to other childhood disorders\textsuperscript{52,53}.

The key frontal disorder-specific abnormality in OCD both in structure and function was in the r/dACC/MPFC, extending previous VBM meta-analyses and mega-analyses\textsuperscript{81,43-45} by showing that this region is also functionally abnormal during inhibitory control and, furthermore, disorder-specifically abnormal relative to ADHD. The r/dACC/MPFC is closely integrated with the striatal and limbic regions and supports top-down affective, behavioral, and cognitive regulation, including inhibitory control\textsuperscript{8,10-14,80,81}. Findings of decreased GMV and activation in the r/dACC/MPFC, together with enhanced basal ganglia/AI structure and function, are consistent with theories of frontostriatal dysregulation, wherein OCD symptoms are proposed to result from impaired top-down MPFC regulation over overactive basal ganglia, resulting in insufficiently controlled repetitive stereotyped behaviors\textsuperscript{5,61,82,83}.

The disorder-contrasting findings also support developmental theories of a delayed development in VLPFC-insular-striatal networks in ADHD\textsuperscript{52,84} but a deviance of frontostriatal development in OCD with overactive and larger basal ganglia being poorly controlled by underdeveloped and underfunctioning medial frontal structures of top-down control\textsuperscript{5,61,82,83}. A mega-analysis of GMV in adults with OCD found that putamen and insula volumes were abnormally preserved with increasing age in patients while they typically decrease in controls, suggesting that abnormalities may become more pronounced with age\textsuperscript{46}. Due to the small number of pediatric OCD studies, the current meta-analytic findings are primarily driven by adult data sets, as is also evident from the high replicability of findings in the adult sub-meta-analyses. Nonetheless, the pediatric VBM sub-meta-analyses still showed disorder-specific increased basal ganglia and insula GMV in patients with OCD relative to those with ADHD, in whom they were decreased relative to controls. Future meta-analyses across larger age ranges, however, will be needed to shed more light on developmental effects.

Shared GMV abnormalities in the vmOFC suggest shared deficits in affect and motivation control\textsuperscript{85-87}. The vmOFC via top-down regulation of the amygdala and ventral striatum mediates fear extinction\textsuperscript{85-87}, emotion interference\textsuperscript{86,89}, cognitive reappraisal\textsuperscript{89}, and reward-related decision making\textsuperscript{89-95}. Underactivation of the vmOFC without VLPFC has been reported in OCD during fear extinction\textsuperscript{85} and reversal learning\textsuperscript{86} and symptom provocation\textsuperscript{76} and in ADHD during emotion/reward processing\textsuperscript{92,97-99} and temporal discounting\textsuperscript{100,101}. Shared GMV deficits in the vmOFC in ADHD and OCD therefore presumably reflect shifted deficits in top-down control over affect and motivation\textsuperscript{80-83,102}, which should be tested in future fMRI studies of such tasks.

The metaregression analyses showed no effects of long-term selective serotonin reuptake inhibitor or stimulant treatment on brain structure in OCD and ADHD, respectively. However, long-term use of stimulant medication in patients with ADHD was associated with bilateral VLPFC/AI and temporal activation and decreased SMA activation. These findings extend our previous meta-analytic finding of increased right VLPFC/insula and reduced SMA activation with acute stimulant doses\textsuperscript{48}. Most importantly, the findings indicate that differences between ADHD and OCD in brain function and structure abnormalities are not attributable to long-term medication effects because stimulant use would have mitigated group differences in these regions.

This study has several limitations, many of which are generally applicable to meta-analyses. The meta-analysis was based primarily on peak coordinates rather than raw statistical brain maps\textsuperscript{48}. Relatedly, studies used different statistical thresholds, and true group differences may be lost from studies reporting at conservative thresholds\textsuperscript{48}. In both imaging modalities, ADHD studies included younger and more male patients. However, findings remained in covariance analyses and in sex- and age-matched adult subgroup meta-analyses. The combination of different fMRI tasks within the inhibitory control domain introduces task-related heterogeneity. However, findings survived when task type was covaried.

Conclusions

In line with current theoretical models, this multimodal meta-analytic comparison shows that both the frontal location and the sign of striatoinsular structure and function deficits differed significantly between patients with ADHD and those with OCD. Functional abnormalities in the VLPFC were disorder-specific to ADHD whereas structural and functional r/dACC/MPFC deficits were disorder specific to OCD. Crucially, abnormalities in bilateral putamen and insula were disorder contrasting, suggesting disorder-differential frontostriatal systems, involving smaller and underfunctioning ventral frontostriatoinsular salience detection/inhibitory networks in ADHD and frontostriatal dysregulation in OCD, where enlarged and overactive insula and putamen may be poorly controlled by smaller and underactive r/dACC/MPFC.

The meta-analytic findings stress distinctive striatal and frontal neurofunctional and neurostructural biomarkers for the 2 disorders, which could have implications for future differential diagnosis and differential treatment. For example, multivariate pattern recognition analyses could be used to test the possibility to differentially diagnose ADHD and OCD on the basis of frontostriatal activation and/or structure patterns. Disorder-specific neurofunctional biomarkers also provide useful targets for treatment with drugs that target these regions or for nonpharmacological therapies such as fMRI-based neurofeedback, brain stimulation, or cognitive training of functions mediated by these regions. While this meta-analysis aimed to understand the shared and differential brain abnormalities in relatively pure disorders, future studies should test to what extent the comorbid cases with both ADHD and OCD differ from the individual disorders.
Meta-Analytic Comparison of Brain Abnormalities in ADHD and OCD

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Study concept and design: Norman, Carlisi, Lukito, Radua, Rubia.

Acquisition, analysis, or interpretation of data: Norman, Carlisi, Lukito, Hart, Mataix-Cols, Radua, Rubia.

Drafting of the manuscript: Norman, Radua, Rubia. Critical revision of the manuscript for important intellectual content: Carlisi, Lukito, Hart, Mataix-Cols, Radua, Rubia.

Statistical analysis: Norman, Carlisi, Radua.

Obtained funding: Rubia.

Administrative, technical, or material support: Carlisi, Rubia.

Study supervision: Mataix-Cols, Rubia.

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