Meta-analytical Comparison of Voxel-Based Morphometry Studies in Obsessive-Compulsive Disorder vs Other Anxiety Disorders

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Context: Whether obsessive-compulsive disorder (OCD) is adequately classified as an anxiety disorder is a matter of considerable debate.

Objectives: To quantitatively compare structural brain changes in OCD and other anxiety disorders using novel voxel-based meta-analytical methods and to generate an online database to facilitate replication and further analyses by other researchers.

Data Sources: The PubMed, ScienceDirect, and Scopus databases were searched between 2001 (the date of the first voxel-based morphometry study in any anxiety disorder) and 2009. All voxel-based morphometry studies comparing patients with any anxiety disorder and healthy controls were retrieved. Manual searches were also conducted. Authors were contacted soliciting additional data.

Study Selection: Thirty-seven data sets were identified, of which 26 (including 639 patients with anxiety disorders and 737 healthy controls) met inclusion criteria.

Data Extraction: Coordinates were extracted from clusters of significant gray matter difference between pa-

tients and controls. Demographic, clinical, and methodological variables were extracted from each study or obtained from the authors.

Data Synthesis: Patients with anxiety disorders (including OCD) showed decreased bilateral gray matter volumes in the dorsomedial frontal/anterior cingulate gyri. Individuals with OCD had increased bilateral gray matter volumes (vs healthy controls and vs individuals with other anxiety disorders) in the lenticular/caudate nuclei, while patients with other anxiety disorders (mainly panic and posttraumatic stress disorders) had decreased gray matter volumes in the left lenticular nucleus. The findings remained largely unchanged in quartile and jackknife sensitivity analyses. Controlling for potential confounders such as age or antidepressant medication had little impact on the results.

Conclusions: The meta-analysis consistently revealed common as well as distinct neural substrates in OCD and other anxiety disorders. These results have implications for the current debate surrounding the classification of OCD in the *DSM-V*.

Arch Gen Psychiatry. 2010;67(7):701-711

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O BSESSIVE-COMPULSIVE DISorder (OCD) is a common and disabling form of mental illness characterized by frequent obsessions and/or compulsions that are associated with high levels of distress and interference. Obsessive-compulsive disorder is currently classified as an anxiety disorder in the *DSM-IV-TR*.[1] In the *International Statistical Classification of Diseases, 10th Revision*,[2] OCD is not listed as an anxiety disorder but remains classified under the broad umbrella of "neurotic, stress-related, and somatoform disorders," thus recognizing the historical interrelationship between OCD and anxiety and their association with psychological distress.

Consistent with this classification, OCD shares many features with other anxiety disorders (OADs), such as excessive fear of disorder-specific situations, dysfunctional overestimation of threat, avoidance/escape and safety-seeking behaviors, and increased physiological arousal.[3] Family studies show that OADs (particularly generalized anxiety disorder and agoraphobia) are more common in relatives of OCD-affected probands than in relatives of control probands, even after controlling for relative OCD diagnosis and proband diagnosis of the same anxiety disorder.[4-6] A recent twin study showed that OCD shares a substantial proportion (55%) of its genetic liability with OADs but also has appreciable disorder-specific genetic and shared environmental influences.[7] Fur-

thermore, OCD and OADs often respond to broadly similar pharmacological (selective serotonin reuptake inhibitors) and psychological (exposure-based) interventions. However, the status of OCD as an anxiety disorder has also been challenged in different ways over the years. Some suggested that OCD may be closer to the affective[8] or even psychotic[9] spectrum of disorders. More recently, a reclassification of OCD has been proposed whereby OCD should be removed from the anxiety disorders category on the basis that OCD is uniquely characterized by the presence of repetitive behaviors and the inability to resist urges and impulses.[10] According to this view, obsessions and compulsions are the core features of OCD and anxiety, simply an epiphenomenon. Furthermore, it is suggested that a new grouping is created that includes OCD as well as other disorders that are thought to share phenomenological and other features with OCD and that are currently classified elsewhere in the *DSM*.[10] Remarkably, a recent survey among worldwide OCD experts revealed a clear lack of consensus regarding whether OCD should remain or be removed from the anxiety disorders category in the *DSM-V*.[11]

The research agenda for the *DSM-V* emphasizes the importance of applying the findings from basic and clinical neurosciences to guide psychiatric classification.[12] Neuroimaging tools have the potential to assist in such endeavors but, surprisingly, direct comparisons of brain function and structure between OCD and OADs are extremely rare.[13,14] This paucity of data is partially because of different traditions in OCD and OADs research and the use of different experimental paradigms making comparisons difficult and precluding the establishment of a solid neuroscientific basis for classification.[15] Indeed, while neuroimaging research in OCD has been long dominated by a focus on the ventral prefrontal-striatal circuits, neuroimaging work in OADs has primarily focused on the amygdala-hippocampus complex and related limbic regions.[15]

Structural magnetic resonance imaging studies are potentially more amenable to comparisons across the anxiety disorders because they are paradigm-free but are not without their problems. Many morphometric studies in OCD and OADs have used manual or semiautomated methods to measure the volumes of brain regions defined a priori as being "abnormal," therefore preventing the exploration of other brain regions potentially implicated in these disorders. The recent advent of fully automated, whole-brain voxel-based morphometry (VBM) methods,[16-18] which overcome some of the limitations of the region of interest approach, provide a powerful and unbiased tool to study the neural substrates of psychiatric disorders. Unfortunately, recent applications of these novel methods are often limited by relatively small sample sizes, resulting in insufficient statistical power and increased risk of false-positive results. Recently developed voxel-based meta-analytical methods have the potential to quantify the reproducibility of neuroimaging findings and to generate insights difficult to observe in isolated studies.[19]

In this study, we conducted an exhaustive search of all published and unpublished VBM studies in all anxiety disorders and applied novel voxel-based meta-analytical methods to examine the extent to which OCD shares neural substrates with OADs. We tested the null hypothesis that no differences in regional gray matter volumes would be found between OCD and OADs. To facilitate replication and further analyses by other colleagues, we have also developed a readily accessible online database that contains all the data and methodological details from every study included in this meta-analysis.

METHODS

INCLUSION OF STUDIES

We conducted exhaustive literature searches of relevant articles published between 2001 (the date of the first VBM study in any anxiety disorder) and 2009 using the PubMed, ScienceDirect, and Scopus databases. The search key words were "anxiety disorder," "obsessive-compulsive disorder," "panic disorder," "agoraphobia," "phobia," and "stress disorder," plus "morphometry," "voxel-based," or "voxelwise." The key word "phobia" was intended to retrieve both specific and social phobias, and the key word "stress disorder" was intended to retrieve both acute stress disorder and posttraumatic stress disorder (PTSD). In addition, we also conducted manual searches of the reference sections of the obtained articles. Studies containing duplicated data sets, ie, analyzed the same data in different articles, and studies with fewer than 9 patients were excluded. Next, the corresponding authors were contacted by e-mail requesting any detail not included in the original manuscripts. MOOSE guidelines for meta-analyses of observational studies[20] were followed in the study.

COMPARISON OF GLOBAL GRAY MATTER VOLUMES

Meta-analytical differences in global gray matter volumes were calculated using random-effects models with the MiMa function[21] in R.[22]

COMPARISON OF REGIONAL GRAY MATTER VOLUMES

Regional differences in gray matter volume between patients and controls were analyzed using Signed Differential Mapping (SDM) (http://www.sdmproject.com), a novel voxel-based meta-analytic approach that is based on and improves on other existing methods[23,24] and also incorporates several novel features. The method has been described in detail elsewhere[25] and is briefly summarized herein.

First, a strict selection of the reported peak coordinates of gray matter differences is applied by only including those that appear statistically significant at the whole-brain level. This is intended to avoid biases toward liberally thresholded brain regions, as it is not uncommon in neuroimaging studies that the statistical threshold for some regions of interest is rather more liberal than for the rest of the brain. Second, a map of the differences in gray matter is separately recreated for each study. This includes limiting voxel values to a maximum to avoid biases toward studies reporting various coordinates in proximity and reconstructing both increases and decreases of gray matter in the same map. Finally, the statistical maps are obtained by calculating the corresponding statistics from the study maps, weighted by the squared root of the sample size of each study so that studies with large sample sizes contribute more. The statistical significance of each voxel is determined using standard randomization tests.[25]

In this study, an omnibus test (Q statistic[26]) was performed to determine if there were differences in gray matter across the different anxiety disorders. Specifically, the Q statistic of the "anxiety disorder" factor was calculated in each voxel as it is usually calculated in standard meta-analyses, with the only difference that its statistical significance was determined by means of a randomization test.[25] Age, percentage of male patients, age at onset, percentage of patients receiving medication, and percentage of patients with comorbid major depressive disorder were considered potential confounders and included as covariates if they showed relevant differences across the different anxiety disorders (Cohen $f \geq 0.27$ for continuous variables; Cramer $\varphi \geq 0.21$ for binary variables). Missing values in these variables were obtained by imputation of the mean of the corresponding disorder. Variables with 20% or more missing values were discarded. Age of patients was included in its linear and quadratic forms (age + age squared, the latter obtained from age mean and variance), as the developmental trajectories of some regions such as the medial prefrontal cortex are not linear.[27] Brain regions with significant main effects of anxiety disorder were used to classify the disorders into 2 (or more) gray-matter–based groups of disorders.

Next, standard SDM meta-analyses[25] were conducted separately in each group of disorders to describe the differences in gray matter between patients and healthy controls. These were complemented with additional analyses to assess the robustness of the findings.[25] These included descriptive analyses of quartiles to find the actual proportion of studies reporting results in a particular brain region (regardless of P values) and jackknife sensitivity analyses to assess the replicability of the results. Finally, we formally tested whole-brain differences in gray matter volume between OCD and OADs by calculating the difference between both groups of disorders in each voxel and determining its statistical significance using a randomization test.[25]

All analyses were conducted twice: first including all samples and subsequently including adult samples only.

RESULTS

INCLUDED STUDIES AND SAMPLE CHARACTERISTICS

As shown in **Figure 1**, the search retrieved a total of 37 studies (17 OCD; 8 panic disorder [PD]; 11 PTSD; 1 various anxiety disorders). Seven studies were discarded because they contained duplicated data sets[28-33] or fewer than 9 patients.[34] Because the samples from 2 studies[35,36] partially overlapped, we conducted the meta-analysis twice, ie, once with each study. Since the results were identical, we only report the results including the first of these studies.[35] After contacting the authors, no methodological ambiguities remained regarding the design or analysis of 26 studies (14 OCD; 5 PD; 6 PTSD; 1 various anxiety disorders), while 4 had to be excluded because of missing key information for our meta-analysis[37-40] (ie, peak coordinates from whole-brain analyses). Therefore, 26 high-quality studies could be included in this meta-analysis, of which 25 were published or accepted for publication and 1 was a previously unpublished subanalysis within a published article (new sample).[32] Twelve of the 14 OCD studies were included in our previous meta-analysis conducted in December 2008.[25]

Combined, the studies included 639 patients with anxiety disorders (430 with OCD, 106 with PD, 86 with PTSD,
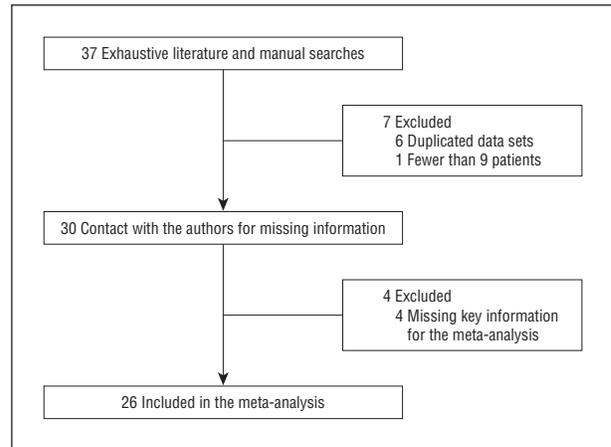

Figure 1. Inclusion of studies.

and 17 patients from a study on various anxiety disorders) and 737 healthy controls. The demographic and clinical characteristics of the participants in each study are shown in **Table 1**. Further details and methodological aspects of each of the included studies can be found at http:/www.sdmproject.com/database.[1]

No relevant differences between patients and controls were found in terms of age and sex, as the original studies were already well matched in this respect (Table 1). Because the age of the patients, as well as the percentage of patients receiving antidepressant medication, moderately varied across the different anxiety disorders (Cohen $f = 0.30$ and Cramer $\varphi = 0.27$, respectively), we controlled for these potential confounds by including age, age squared, and percentage of patients receiving antidepressant medication as covariates in the omnibus test. Other reported medications were infrequent: anxiolytics (4.7%), amphetamines (0.5%), antipsychotics (n=1), guanfacine hydrochloride (n=1), lithium (n=1), and thyroxine (n=1). The percentages of male and depressed patients were rather similar in the different disorders (Cramer $\varphi = 0.09$ and 0.11, respectively) and thus not included as covariates. Mean age at onset could not be considered because of a large proportion (44%) of missing values.

Regarding comorbidity, 3.5% patients from OCD studies and 5.6% patients from PTSD studies had comorbid PD. One patient from a PTSD study had comorbid OCD, and 1 patient from an OCD study had comorbid PTSD. With the exception of major depressive disorder (Table 1), other individual comorbid disorders were relatively infrequent: generalized anxiety disorder, 6.3%; social phobia, 4.9%; and specific phobias, 1.9%.

GLOBAL DIFFERENCES IN GRAY MATTER VOLUME

Global gray matter volumes were obtained from 13 studies* (9 OCD; 2 PD; 2 PTSD). Comparisons across disorders and analyses in individual disorders other than OCD were not possible, as there were too few PD and PTSD studies for analysis. No statistically significant differences in global gray matter volume were found be-

*References 35, 41, 45-48, 50-53, 55, 57, 60.

Table 1. Demographic and Clinical Characteristics of the 26 Voxel-Based Morphometry Studies Included in the Meta-analysis

Source	Patients					Controls		
	Sample Size	Age, y, Mean (SD)	Males, %	Antidepressant Treatment, %	Comorbid MDD, %	Sample Size	Age, y, Mean (SD)	Males, %
OCD studies								
Carmona et al[41]	18	12.9 (2.8)	72	56	0	18	13.0 (3.0)	72
Christian et al[42]	21	38.0 (9.6)	71	81	33	21	38.9 (9.8)	71
Gilbert et al[43]	25	37.5 (10.7)	52	80	36	20	29.8 (7.9)	45
Gilbert et al[44]	10	12.9 (2.7)	60	0	0	10	13.4 (2.6)	60
Kim et al[45]	25	27.4 (7.0)	68	0	16	25	27.0 (6.2)	68
Koprivová et al[46]	14	28.6 (6.1)	36	71	0	15	28.7 (6.5)	40
Lázaro et al[47]	15	13.7 (2.5)	53	0	0	15	14.3 (2.5)	53
Pujol et al[48]	72	29.8 (10.5)	56	75	36	72	30.1 (10.2)	56
Riffkin et al[49]	18	36.1 (13.0)	44	17	NA	18	34.5 (11.8)	44
Soriano-Mas et al[32]	30	31.9 (9.3)	70	87	13	30	31.8 (10.2)	53
Szeszko et al[50]	37	13.0 (2.7)	38	0	0	26	13.0 (2.6)	35
Valente et al[51]	19	32.7 (8.8)	53	58	47	15	32.3 (11.8)	47
van den Heuvel et al[52]	55	33.7 (9.2)	29	0	18	50	31.4 (7.6)	40
Yoo et al[53]	71	26.6 (7.5)	66	83	6	71	26.7 (6.1)	66
Subtotal	430	27.9 (11.5)	54	49	18[a]	406	27.4 (10.5)	54
PD studies								
Asami et al[35]	24	37.0 (10.2)	38	80	13	24	37.0 (9.5)	38
Hayano et al[36]	27	38.2 (9.9)	37	89	11	30	35.3 (10.5)	30
Massana et al[54]	18	36.8 (11.3)	39	NA	0	18	36.7 (8.8)	44
Uchida et al[55]	19	37.1 (9.8)	16	74	63	20	36.5 (9.9)	20
Yoo et al[56]	18	33.3 (7.1)	50	NA	0	18	32.0 (5.8)	61
Subtotal[b]	79	36.1 (9.7)	35	77[a]	19	80	35.7 (8.8)	40
PTSD studies								
Carrion et al[57]	19	11.5 (3.7)	58	26	11	22	11.1 (2.6)	55
Chen et al[58]	12	34.6 (4.9)	33	0	0	12	33.2 (5.3)	33
Corbo et al[59]	14	33.4 (12.1)	43	0	50	14	33.3 (12.3)	43
Hakamata et al[60]	14	45.6 (6.2)	0	0	50	100	47.1 (5.7)	0
Kasai et al[61]	18	52.8 (3.4)	100	NA	56	23	51.8 (2.3)	100
Yamasue et al[62]	9	44.6 (16.0)	56	0	11	16	44.4 (14.0)	63
Subtotal	86	35.9 (16.7)	51	7[a]	31	187	41.3 (14.0)	29
Various anxiety disorders								
Milham et al[63]	17	12.9 (2.3)	47	0	24	34	12.4 (2.2)	47

Abbreviations: MDD, major depressive disorder; NA, not available; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder.
[a] Result obtained after imputation of missing values using the mean of the corresponding disorder.
[b] Result obtained after excluding the study by Hayano et al.[36]

tween patients with OCD (n=326) and healthy controls (n=307) (unbiased Hedges[64] $d=-0.19$; $z=-1.51$; $P=.13$). The same results emerged when the 3 pediatric OCD studies were excluded from the analysis (unbiased Hedges $d=-0.15$; $z=-1.61$; $P=.11$).

REGIONAL DIFFERENCES IN GRAY MATTER VOLUME ACROSS ANXIETY DISORDERS

Data for this analysis were obtained from 24 studies (14 OCD; 4 PD; 6 PTSD) including 595 patients (430 OCD; 79 PD; 86 PTSD) and 673 healthy controls. There was a main effect of anxiety disorder factor on gray matter volume in the left lenticular nucleus (mainly the anterior putamen) and right caudate extending to the lenticular nucleus (mainly the anterior putamen) (**Table 2**). When age was introduced as a linear covariate, the results remained unchanged but additional differences were also observed in a small bilateral region in the ventromedial frontal gyri and Brodmann area 11/32 (Talairach coordinates [x, y, z], 4, 32, –12; $P<.001$; 46 voxels). When quadratic age (ie,

age + age squared) or the percentage of patients receiving antidepressant medication were introduced in the model, the results remained unchanged, ie, only the left lenticular and right caudate (extending to lenticular) nuclei were significantly different across anxiety disorders. Finally, when 6 pediatric studies were excluded, the results also remained unchanged.

These omnibus tests were followed by inspection of gray matter volumes in the basal ganglia in OCD, PD, and PTSD. As shown in Table 2 and **Figure 2**, patients with OCD showed increased gray matter in the bilateral lenticular/caudate nuclei compared with controls, while both PD and PTSD showed decreased gray matter volume in these regions compared with controls.

REGIONAL DIFFERENCES IN GRAY MATTER VOLUME: OCD VS HEALTHY CONTROLS

Data for this analysis were obtained from all 14 studies on OCD, representing 430 patients and 406 healthy controls. Consistent with our previous meta-analysis, which

Table 2. Regions With Significant Differences in Gray Matter Volumes Across Anxiety Disorders (Omnibus Test)[a]

	Talairach Coordinates, x, y, z	P Value[b]	No. of Voxels[c]	OCD vs Controls	PD vs Controls	PTSD vs Controls
Left lenticular nucleus (mainly anterior putamen)	−24, 6, 0	<.001	286	+0.210	−0.199	−0.215
Right caudate head (extending to lenticular nucleus)	14, 16, 0	<.001	287	+0.143	−0.368	−0.009

Abbreviations: OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder; SDM, Signed Differential Mapping.
[a] Values in the OCD, PD, and PTSD columns represent the difference in gray matter volume (SDM value) in patients vs controls. Positive values represent increases and negative values represent decreases.
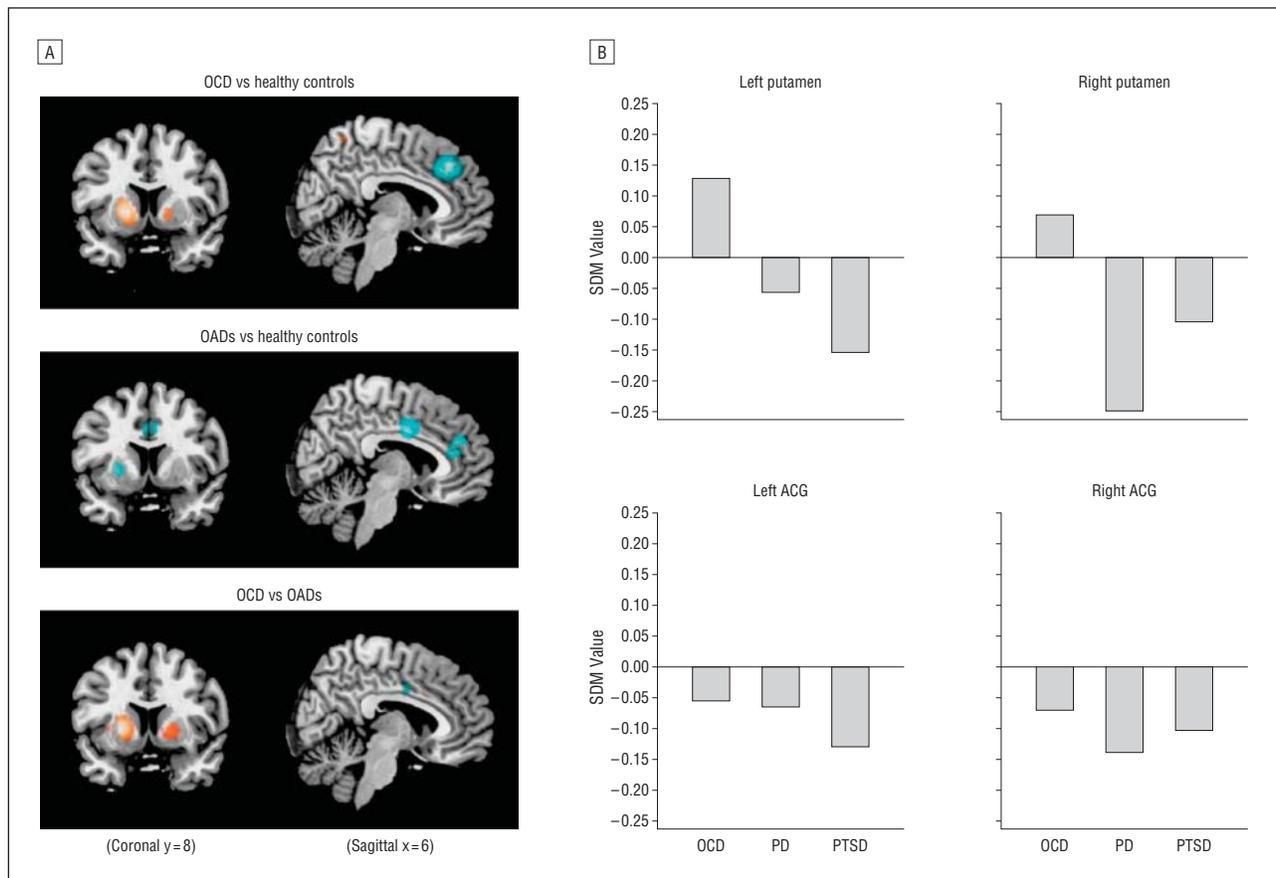[b] P values were obtained from a randomization test.[25]
[c] 1 voxel = 8 mm[3].

Figure 2. Common and distinct neural correlates in obsessive-compulsive disorder (OCD) and other anxiety disorders (OADs). A, The coronal slices show significant differences across the different anxiety disorders in the bilateral lenticular nuclei (mainly the anterior putamen), with increased gray matter volume (orange) in OCD (first row) and decreased volume (cyan) in OADs (second row). The formal comparison between OCD and OADs confirmed these differences (third row). The sagittal slices show similarly decreased gray matter volumes in the dorsomedial frontal gyrus/anterior cingulate gyrus (ACG) region in the different anxiety disorders. Statistical threshold was set at $P \le .001$ and significant clusters have been overlaid on an MRIcron template (http://www.cabiatl.com /mricro/mricron/) for display purposes only. B, The bar graphs show the Signed Differential Mapping (SDM) values of gray matter volume (as compared with healthy controls) in the putamen (first row) and ACG (second row) in each disorder derived from the omnibus test. PD indicates panic disorder; PTSD, posttraumatic stress disorder.

included 12 of the 14 OCD studies available at that time,[25] patients with OCD showed robust increased regional gray matter volumes in the bilateral lenticular/caudate nuclei and right superior parietal lobule. Decreased gray matter volumes were found in the bilateral dorsomedial frontal gyrus (dMFG)/anterior cingulate gyrus (ACG) (**Table 3** and Figure 2). Results were similar after exclusion of 4 pediatric OCD studies, with increased gray matter volumes in the left lentiform/caudate nucleus and decreased gray matter volumes in the bilateral dMFG/ACG.

The results remained largely unchanged in the analysis of quartiles with the exception of the superior parietal lobule, which was no longer significant. Whole-brain jackknife sensitivity analysis showed that the gray matter increase in the left lenticular nucleus was highly replicable, as this finding was preserved in all combinations of studies. Gray matter decrease in the dMFG/ACG emerged in all but one combination of studies, whereas gray matter increases in the right lenticular nucleus and superior parietal lobule emerged in all but 2 combinations of studies.

Table 3. Regions With Significant Differences in Gray Matter Volume Between Patients With OCD and Healthy Controls

	Maximum			Cluster[a]	
	Talairach Coordinates, x, y, z	SDM Value	P Value[b]	No. of Voxels	Breakdown (No. of Voxels)
Clusters of increased gray matter					
Left lenticular/caudate nuclei (mainly anterior putamen)	−18, 8, 0	+0.226	<.001	517	Left putamen (390) Left pallidum (64) Left caudate nucleus (44)
Right superior parietal lobule	14, −58, 60	+0.182	<.001	66	Right BA 7 (66)
Right lenticular/caudate nuclei (mainly anterior putamen)	18, 10, −2	+0.173	<.001	99	Right putamen (74) Right caudate (16)
Clusters of decreased gray matter					
Bilateral dMFG/ACG	2, 30, 38	−0.257	<.001	426	Bilateral BA 8 (170) Bilateral BA 32 (140) Bilateral BA 6 (70) Bilateral BA 9 (46)

Abbreviations; ACG, anterior cingulate gyrus; BA, Brodmann area; dMFG, dorsomedial frontal gyrus; OCD, obsessive-compulsive disorder; SDM, Signed Differential Mapping.
[a] Regions smaller than 10 voxels are not shown. 1 voxel = 8 mm^3.
[b] P values were obtained from a randomization test.[25]

Table 4. Regions With Significant Differences in Gray Matter Volume Between Patients With OADs and Healthy Controls

	Maximum			Cluster[a]	
	Talairach Coordinates, x, y, z	SDM Value	P Value[b]	No. of Voxels	Breakdown (No. of Voxels)
Clusters of increased gray matter (none)					
Clusters of decreased gray matter					
Bilateral dMFG/ACG	−2, 36, 20	−0.266	<.001	231	Bilateral BA 32 (116) Bilateral BA 9 (80) Bilateral BA 24 (35)
Bilateral posterior part of the ACG	4, 0, 34	−0.251	<.001	205	Bilateral BA 24 (205)
Left lenticular nucleus (mainly anterior putamen)	−26, 4, 0	−0.238	<.001	65	Left putamen (62)

Abbreviations: ACG, anterior cingulate gyrus; BA, Brodmann area; dMFG, dorsomedial frontal gyrus, OADs, other anxiety disorders; SDM, Signed Differential Mapping.
[a] Regions smaller than 10 voxels are not shown. 1 voxel = 8 mm^3.
[b] P values were obtained from a randomization test.[25]

REGIONAL DIFFERENCES IN GRAY MATTER VOLUME: OADs VS HEALTHY CONTROLS

Because the omnibus test (Q statistic) revealed similar neural substrates in PD and PTSD, these disorders were collapsed together to form a new group called OADs and used in all subsequent analyses. This group also included the study by Milham et al[63] on various pediatric anxiety disorders, making a total of 11 studies representing 199 patients and 301 healthy controls. As shown in **Table 4** and Figure 2, individuals with OADs had significant gray matter volume decreases in the bilateral dMFG/ACG, bilateral posterior part of the ACG, and left lenticular nucleus (mainly the rostral putamen). No increases of gray matter volume were detected. The results did not change when the study by Milham et al[63] or the 2 pediatric studies were excluded, but additional decreases of gray matter volume were also observed in the right insula extending to the lentiform nucleus (Talairach coordinates [x, y, z], 40, −8, 2; SDM = −0.256; P = .001; 24 voxels) and the left middle tem-

poral gyrus, Brodmann area 21/22 (Talairach coordinates [x, y, z], −52, −42, 6; SDM = −0.254; P = .001; 17 voxels).

In the quartiles/median analysis, decreases of gray matter were detected in the bilateral dMFG/ACG and bilateral lenticular/caudate nuclei, meaning that most of the studies had found some degree of decreased gray matter in or near these regions. No increases of gray matter were detected in the quartiles analyses. Finally, whole-brain jackknife sensitivity analysis showed that the gray matter decrease in the bilateral dMFG/ACG was highly replicable, as these findings were preserved in 9 of the 11 combinations of studies. Gray matter decreases in the bilateral posterior part of the ACG and left lenticular nucleus emerged in all but 3 combinations of studies.

REGIONAL DIFFERENCES IN GRAY MATTER VOLUME: OCD VS OADs

The formal comparison between OCD and OADs largely confirmed the earlier-mentioned findings (**Table 5** and

Table 5. Regions With Significant Differences in Gray Matter Volume Between Patients With OCD and Patients With OADs

	Maximum			Cluster[a]	
	Talairach Coordinates, x, y, z	SDM Value	P Value[b]	No. of Voxels	Breakdown (No. of Voxels)
OCD>OADs					
Left lenticular nucleus (mainly anterior putamen)	−24, 6, 0	0.436	Undetectable	651	Left putamen (472) Left pallidum (109) Left claustrum (43) Left caudate nucleus (15)
Right lenticular nucleus (mainly anterior putamen)	18, 10, −2	0.315	<.001	392	Right putamen (213) Right caudate nucleus (103) Right pallidum (74)
OADs>OCD					
Right dMFG/ACG	6, 24, 38	0.195	<.001	43	Right BA 8 (22) Right BA 32 (19)

Abbreviations: ACG, anterior cingulate gyrus; BA, Brodmann area; dMFG, dorsomedial frontal gyrus; OADs, other anxiety disorders; OCD, obsessive-compulsive disorder; SDM, Signed Differential Mapping.
[a] Regions smaller than 10 voxels are not shown. 1 voxel=8 mm^3.
[b] P values were obtained from a randomization test.[25]

Figure 2). Patients with OCD had significantly greater gray matter volumes than patients with OADs in the bilateral lenticular/caudate nuclei and lower gray matter volumes in a small region in the right dMFG/ACG. The age, percentage of male patients, percentage of patients receiving an antidepressant medication, and percentage of depressed patients were comparable between OCD and OADs (Cohen ƒ=0.22 and Cramer φ=0.07, 0.08, and 0.08, respectively) and thus not included as covariates. The results remained largely unchanged after exclusion of 6 pediatric studies, with the exception that patients with OCD had significantly greater gray matter volumes in another small region in the bilateral dMFG/ACG, Brodmann area 24 (Talairach coordinates [x, y, z], −2, −4, 34; SDM=−0.308; P<.001; 53 voxels).

COMMENT

While OCD is currently classified as an anxiety disorder in the *DSM-IV-TR*, there is a substantial disagreement in the field as to whether this should be retained in the *DSM-5* or whether OCD should be removed from the broad umbrella of anxiety disorders and placed elsewhere.[3,10,11] The neurosciences have the potential to assist classification efforts by mapping the common and distinct neural substrates of mental disorders. Several major conclusions can be drawn from the present meta-analysis of VBM studies.

SHARED NEURAL SUBSTRATES IN OCD AND OADs

Patients with OCD and OADs showed decreased bilateral regional gray matter volumes in the dMFG/ACG compared with healthy controls. These findings were very robust as they consistently emerged using multiple statistical approaches and various sensitivity and subgroup analyses. A plethora of evidence from animal, lesion, and neuroimaging studies indicates that the dMFG/ACG is implicated in the mediation or modulation of both normal and pathological anxiety. For example, in humans, direct stimulation of the ACG evokes anxiety.[65] The thickness and degree of activation of the dorsal ACG are positively correlated with skin conductance responses during fear conditioning in healthy individuals.[66] Activation of this region is consistently seen during the processing of threat-related as well as other emotion-relevant stimuli[67,68] and seems important for the cognitive regulation of emotions.[69-71] The dorsal ACG also plays a key role in error monitoring, a process that may be common to most anxiety disorders, including OCD.[72-74] Activation in different ACG regions and the medial prefrontal cortex is associated with anticipatory anxiety both in healthy individuals[75,76] and patients with anxiety disorders.[77] Functional neuroimaging studies of anxiety disorders, including OCD, have consistently found hyperactivation in the dMFG/ACG region using various symptom provocation procedures.[13,78-85] This hyperactivity is at least partially reversible with cognitive behavior therapy.[86,87] Finally, the dorsal ACG region implicated in this meta-analysis corresponds to the target of anterior cingulotomy, an ablative surgical treatment that alleviates severe obsessive-compulsive symptoms, anxiety, and depression.[88] Taken together, these multiple lines of evidence suggest that this brain region is commonly implicated in all anxiety disorders, including OCD.

DIFFERENCES BETWEEN OCD AND OADs

Compared with healthy controls, individuals with OCD had increased bilateral regional gray matter volumes in the lenticular nuclei (mainly the ventral anterior putamen) extending to the caudate nuclei. Conversely, patients with OADs had decreased gray matter volumes (vs healthy controls) in the left lenticular nucleus (mainly the ventral anterior putamen). The study of the differences in gray matter volume across the different anxiety disorders confirmed these findings: patients with OCD had increased bilateral gray matter volumes in the len-

ticular nuclei, extending to the caudate on the right side, in comparison with OADs. These findings appeared to be robust as demonstrated by our descriptive analyses of medians and quartiles. The findings also remained largely unchanged when each study was removed from the analyses "only one at a time" (jackknife sensitivity analysis) and when controlling for potential confounds such as age or antidepressant medication use.

The basal ganglia have long been hypothesized to play a key role in the mediation of obsessive-compulsive symptoms.[89] Indirect evidence is available from focal lesion studies, disorders of known basal ganglia pathology, and, more recently, neuroimaging studies.[15,78,90,91] Conversely, the role of the basal ganglia in OADs has been largely neglected so far. This may be because of different research traditions in OCD vs OADs.[15] The results of this meta-analysis suggest that the basal ganglia are implicated in OADs too, though the direction of the results is opposite to that in OCD. The functional significance of these findings is unclear but it may be a reflection of unique features of OCD vs OADs. One obvious possibility is that increased basal ganglia volumes reflect the repetitive nature of compulsions, which are pathognomonic in OCD. We have recently reported a meta-regression analysis showing a significant positive correlation between the volume of the basal ganglia and the severity of OCD symptoms (scores on the Yale-Brown Obsessive Compulsive Scale).[25] Conversely, Yoo et al[56] reported a significant negative correlation between the duration and severity of panic disorder symptoms and bilateral putamen volume.

The identified region is anatomically very close to the usual targets of psychosurgical interventions for severe anxiety and depression, such as capsulotomy[92,93] and deep brain stimulation.[94,95] Our findings of increased gray matter volume in OCD and decreased gray matter volume in OADs suggest that these ablative procedures may be effective through the disruption of different pathological mechanisms. Indeed, these are relatively crude interventions that may result in anxiety reduction by restoring the balance of activity in the basal ganglia regardless of the exact nature of the dysfunction.

This meta-analysis did not reveal consistent changes in limbic regions, such as the amygdala and hippocampus, in OADs. These changes would be expected from the existing PTSD[96-98] and PD[99] literature. This may be related to limitations inherent to the VBM method. Indeed, standard VBM may not be as sensitive as manual segmentation methods or newer automated algorithms to detect volume changes in these regions.[100] It is also possible that the high smoothing commonly used in VBM studies contributes to the poor sensitivity for volumetric changes in the small limbic structures.[30]

STRENGTHS AND LIMITATIONS

The main strengths of this study are the unbiased inclusion of published as well as unpublished studies, even if their results were negative (ie, when no significant differences between patients and controls were found), and the use of a novel voxelwise meta-analytic method.[25] This method has been further developed by the introduction

of a new statistical approach for voxel-based meta-analysis, ie, testing differences across different disorders with the Q statistic.[26] This is an important new feature that effectively allows finding those brain regions in which significant differences exist across several disorders. Given the complexity of the classification of psychiatric disorders, this method should be useful to researchers planning to undertake meta-analytical comparisons between disorders, ie, beyond simple binary comparisons. To facilitate replication and further analyses by other colleagues, we have developed an online database that contains all the data and methodological details from every study included in this meta-analysis and that is readily accessible at http://www.sdmproject.com/database.

There are several limitations of this study, some of which are inherent to all meta-analytical approaches. First, despite our attempts to contact worldwide OCD and anxiety experts and include as many unpublished VBM studies as possible, even if their results were negative, the possibility of publication bias cannot be entirely ruled out. Second, voxel-based meta-analyses are based on summarized (ie, coordinates from published studies) rather than raw data and this may result in less accurate results.[101] However, obtaining the raw images from the original studies is logistically difficult. Third, while our method provides excellent control for false-positive results, it is more difficult to completely avoid false-negative results. As mentioned earlier, VBM may lack sufficient sensitivity to detect differences in small limbic structures of relevance to anxiety disorders such as the hippocampus and the amygdala.[30,100] Fourth, almost no data from some OADs, such as generalized anxiety disorder or specific phobias, are available.[63] We encourage other researchers to publish their VBM results in these disorders, even if these results do not conform to a priori hypotheses. Finally, separate analyses of pediatric studies could not be performed because of the insufficient number of studies. The latter is important given the likely developmental effects on the neural systems underlying anxiety disorders.[102] When we controlled for age in the omnibus test, we were able to detect possible differences across the anxiety disorders in the ventromedial frontal gyri, though these findings should be interpreted with caution given that most of the studies included adult samples with a limited mean age range (27-38 years).

CONCLUSIONS

To conclude, the results of this meta-analysis suggest common as well as distinct neural substrates in OCD and OADs. Both types of disorders are characterized by volumetric gray matter reductions in the dMFG/ACG, a finding that is entirely consistent with numerous sources of evidence linking this brain structure with both normal and pathological anxiety. While the basal ganglia seem implicated both in OCD and OADs, the direction of the findings is diametrically opposite: OCD is characterized by increased gray matter volume in the basal ganglia whereas OADs are characterized by decreased gray matter volume in the basal ganglia, perhaps suggesting a com-

mon neural substrate but distinct neural mechanisms. In this regard, OCD and OADs may be conceptualized as opposite ends of a neurobiological spectrum. The functional significance of this finding is unclear but since the volume of the basal ganglia correlates with the severity of OCD,[25] it may reflect the unique repetitive nature of compulsions, which are pathognomonic to OCD.

The results have implications for the current debate surrounding the classification of OCD in *DSM-5*. Since there are neurobiological similarities as well as differences between OCD and OADs, our results support maintaining the current classification of OCD as an anxiety disorder while acknowledging its uniqueness. This conclusion is consistent with the current recommendations by the *DSM-5* Anxiety, Obsessive-Compulsive Spectrum, Posttraumatic, and Dissociative Disorders Work Group.[103,104] Specifically, one proposal is to change the name of the anxiety disorders grouping to reflect the inclusion of both anxiety and obsessive-compulsive disorders as partially independent but closely related entities (eg, "anxiety and obsessive-compulsive disorders").[104] Another, not incompatible, proposal is to also broaden this category to include other OCD and anxiety-related disorders, such as body dysmorphic disorder, hypochondriasis, or hoarding disorder (eg, "anxiety and obsessive-compulsive spectrum disorders").[103,105] A similar approach is already adopted by *International Statistical Classification of Diseases, 10th Revision*,[2] and would have the obvious advantage of bringing the *DSM* and *International Statistical Classification of Diseases* systems closer together.

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