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Negative Valence in Obsessive-Compulsive Disorder: A Worldwide Mega-Analysis of Task-Based Functional Neuroimaging Data of the ENIGMA-OCD Consortium

Nadza Dzinalija, Chris Vriend, Lea Waller, H. Blair Simpson, Iliyan Ivanov, Sri Mahavir Agarwal, Pino Alonso, Lea L. Backhausen, Srinivas Balachander, Aniek Broekhuizen, Miguel Castelo-Branco, Ana Daniela Costa, Hailun Cui, Damiaan Denys, Isabel Catarina Duarte, Goi Khia Eng, Susanne Erk, Sophie M.D.D. Fitzsimmons, Jonathan Ipser, Fern Jaspers-Fayer, Niels T. de Joode, Minah Kim, Kathrin Koch, Jun Soo Kwon, Wieke van Leeuwen, Christine Lochner, Hein J.F. van Marle, Ignacio Martinez-Zalacain, Jose M. Menchon, Pedro Morgado, Janardhanan C. Narayanaswamy, Ian S. Olivier, Maria Picó-Pérez, Tjardo S. Postma, Daniela Rodriguez-Manrique, Veit Roessner, Oana Georgiana Rus-Oswald, Venkataram Shivakumar, Carles Soriano-Mas, Emily R. Stern, S. Evelyn Stewart, Anouk L. van der Straten, Bomin Sun, Sophia I. Thomopoulos, Dick J. Veltman, Nora C. Vetter, Henny Visser, Valerie Voon, Henrik Walter, Ysbrand D. van der Werf, Guido van Wingen, ENIGMA-OCD Consortium, Dan J. Stein, Paul M. Thompson, Ilya M. Veer, and Odile A. van den Heuvel

ABSTRACT

OBJECTIVE: Obsessive-compulsive disorder (OCD) is associated with altered brain function related to processing of negative emotions. To investigate neural correlates of negative valence in OCD, we pooled functional magnetic resonance imaging data of 633 individuals with OCD and 453 healthy control participants from 16 studies using different negatively valenced tasks across the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) Consortium's OCD Working Group.

METHODS: Participant data were processed uniformly using HALFpipe, to extract voxelwise participant-level statistical images of one common first-level contrast: negative versus neutral stimuli. In preregistered analyses, parameter estimates were entered into Bayesian multilevel models to examine whole-brain and regional effects of OCD and its clinically relevant features—symptom severity, age of onset, and medication status.

RESULTS: We provided a proof of concept that participant-level data can be combined across several task paradigms and observed one common task activation pattern across individuals with OCD and control participants that encompasses frontolimbic and visual areas implicated in negative valence. Compared with control participants, individuals with OCD showed very strong evidence of weaker activation of the bilateral occipital cortex ($P+ < 0.001$) and adjacent visual processing regions during negative valence processing that was related to greater OCD severity, late onset of the disorder, and an unmedicated status. Individuals with OCD also showed stronger activation in the orbitofrontal, subgenual anterior cingulate, and ventromedial prefrontal cortex (all $P+ < 0.1$) that was related to greater OCD severity and late onset.

CONCLUSIONS: In the first mega-analysis of this kind, we replicated previous findings of stronger ventral prefrontal activation in OCD during negative valence processing and highlight the lateral occipital cortex as an important region implicated in altered negative valence processing.

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Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts or images (obsessions) and/or ritualized behaviors or mental acts (compulsions) that may cause significant distress. A hallmark of the disorder is the impaired processing of negative emotion, both in the form of acute emotional distress and the sustained feelings of potential threat that accompany the

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disorder. Emotional impairment is frequently observed during negatively valenced tasks, particularly symptom provocation tasks designed to trigger an individual's OCD cognitions or behaviors. Neuroimaging studies on this emotional impairment have pointed to the involvement of the frontolimbic circuit that encompasses the amygdala and ventromedial prefrontal cortex (vmPFC) (1). The negative valence domain of the Research Domain Criteria (2) is specifically relevant for OCD in organizing the current understanding of emotional dysfunction and studying the neurobiological basis of that dysfunction in OCD.

Two recent coordinate-based meta-analyses of the neural processing of negative valence in OCD reported mixed effects. Thorsen *et al.* (3) investigated a broad range of negatively valenced tasks across 25 studies and found that individuals with OCD (relative to healthy control participants [HCs]) showed stronger activation of the bilateral amygdala, right orbitofrontal cortex (OFC) (extending into the subgenual anterior cingulate cortex [sgACC] and vmPFC), right putamen, left inferior occipital gyrus, and right middle temporal gyrus (MTG) in response to negatively valenced stimuli. This pattern was associated with greater OCD severity, longer illness duration, and current medication usage. No regions were found to be hypoactive. Conversely, Yu *et al.* (4), using 12 symptom provocation studies that compared people with OCD and HCs, showed stronger activation in the right caudate, putamen, and insula and weaker activation in the left OFC, left inferior frontal gyrus, right MTG, middle occipital gyrus, right lateral occipital cortex (LOC), and left caudate and middle cingulate cortex in response to symptom-triggering stimuli. The coordinate-based meta-analytic approach that these studies used could explain their divergent results despite a partially overlapping sample; when individual studies report activation in a binary all-or-nothing way, subthreshold activations are discarded that are important for reproducible meta-analyses (5).

While meta-analyses bring us closer to approximating true effects (6), large-scale studies that combine individual participant-level data from a large and representative cohort of clinically diverse individuals with OCD are needed to provide sufficient power and address the heterogeneity of OCD. The ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) Consortium's OCD Working Group was founded to address this need and previously investigated cortical and subcortical structure, white matter integrity, and resting-state functional connectivity in OCD (7). These studies allowed investigation of clinical heterogeneity and emphasized the prominent contribution of medication status to brain structure and function. In the first mega-analysis of functional activity across task paradigms, we investigated the clinical features of OCD in relation to negative valence, a cognitive domain relevant for treatment due to its connection to exposure therapy. We hypothesized that individuals with OCD would exhibit stronger frontolimbic activity than HCs in response to negatively valenced stimuli. Because antidepressant medication tends to blunt the limbic hyperresponse observed in individuals with OCD (3,8), we expected to see the most prominent frontolimbic effects in unmedicated individuals. Furthermore, we hypothesized that greater symptom severity and earlier OCD onset would be associated with stronger frontolimbic activation because earlier onset of OCD is predictive of a more chronic trajectory with greater symptom severity (9).

METHODS AND MATERIALS

Study Population

Data were obtained from the ENIGMA Consortium's OCD Working Group, an international network of institutes that have collected brain imaging and clinical data from individuals with OCD and HCs. Sixteen independent samples (9 unpublished) from 11 countries across 4 continents contributed to a total sample of 680 people with OCD and 483 age- and sex-matched HCs. OCD diagnosis was determined by DSM criteria using diagnostic tools administered by trained personnel (Table S1). OCD severity was measured using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) or children's version (CY-BOCS) (10,11). HCs were free of psychopathology and were not currently taking psychotropic medication. Participants gave informed consent at each participating site, and protocols were approved by local institutional review boards, which permitted the use of extracted measures from de-identified participant data.

Negative Valence Tasks

Each sample completed a task with negatively valenced stimuli, which broadly fell into the following categories: symptom provocation (8 tasks), emotion regulation (3 tasks), emotional faces (2 tasks), or other tasks with negative emotional induction or distraction (3 tasks) (Table 1). Although each paradigm differed in conditions and stimuli, each task used visual presentation of negatively valenced stimuli and neutrally valenced stimuli. Negatively valenced stimuli were either designed to provoke obsessive-compulsive symptoms (e.g., dirty surfaces, asymmetrical scenes, active electrical appliances) or were generally threatening (e.g., wounds, weapons, fearful faces). Neutrally valenced stimuli were either neutral images or videos (e.g., nature scenes) or scrambled versions of negatively valenced stimuli. We defined one common contrast across all tasks: negative versus neutral stimuli.

Magnetic Resonance Image Acquisition and Processing

Sites had acquired data using scan parameters shown in Table S2. Because there was no prospective harmonized magnetic resonance imaging data acquisition, we harmonized image processing across samples using the open-source containerized HALFpipe (Harmonized AnaLysis of Functional MRI pipeline) version 1.2.2 (12) built using fMRIprep version 20.2.7 (13) to preprocess the structural and functional images and define the task contrasts of interest. All preprocessing was performed with default settings within HALFpipe, which for structural images included skull stripping, tissue segmentation, and spatial normalization. For functional images, preprocessing included motion correction (and motion parameter extraction), slice time correction (if slice acquisition order was known), susceptibility distortion correction (if fieldmaps were available), coregistration, spatial normalization to Montreal Neurological Institute (MNI) 152 NLIN 2009c (asymmetrical) space and resliced to 2 mm^3, denoising with ICA-AROMA (Independent Component Analysis–based Automatic Removal Of Motion Artifacts) (14), and smoothing with a 6-mm full width at half maximum Gaussian kernel.

Table 1. Task and Contrast Characteristics of Studies Included in the Mega-Analysis

Site, Sample, Reference	Task	OCD, *n*	HC, *n*	Stimuli	OCD-Relevant Aversive Content	General Threat Content	Neutral Content	Event Duration, Seconds	Main Contrast: Negative > Neutral	Contrast: Threat > Neutral	Symptom Provocation Tasks	
											Contrast: OCD > Neutral	Contrast: OCD > Threat
Amsterdam, the Netherlands: Sample I	Symptom provocation	100	52	Images	Wash, check, order	Scenes	Scrambled	3	OCD+threat > neutral	√	√	√
Amsterdam, the Netherlands: Sample II (45)	Emotion regulation	41	35	Images	Wash, check, order	Scenes	Scrambled	5	OCD+threat > neutral	√	√	√
Amsterdam, the Netherlands: Sample III	Symptom provocation	20	19	Images	Wash, check, order	Scenes	Scenes	3.5	OCD+threat > neutral	√	√	√
Amsterdam, the Netherlands: Sample IV	Symptom provocation	32	18	Images	Wash, check, order	Scenes	Scenes	3.5	OCD+threat > neutral	√	√	√
Bangalore, India (46)	Symptom provocation	35	30	Images	Wash, check, order	Scenes	Scenes	2	OCD+threat > neutral	√	√	√
Barcelona, Spain (47,48)	Emotional faces	80	47	Faces	–	Fearful faces	Shapes	5	Threat > neutral	√	–	–
Braga, Portugal: Sample I (49)	Emotion regulation	29	26	Images	–	Scenes	Scenes	5	Threat > neutral	√	–	–
Braga, Portugal: Sample II	Memory task with contamination images	22	0	Images	Wash	–	Scenes	5	OCD > neutral	–	√	–
Cape Town, South Africa	Emotional faces	23	20	Faces	–	Fearful faces	Shapes	5	Threat > neutral	√	–	–
Coimbra, Portugal (50)	Symptom provocation	15	13	Videos/In-bore tactile stimulation	Wash, check, order, bad thoughts	–	Scenes	30	OCD > neutral	–	√	–
Dresden, Germany	Emotion regulation	44	46	Images	–	Scenes	Scenes	5	Threat > neutral	√	–	–
Munich, Germany (51)	Symptom provocation	38	36	Images	Wash	–	Scenes	6	OCD > neutral	–	√	–
New York, United States	Symptom provocation	84	41	Images	Wash, check, order, bad thoughts	Scenes	Scenes	5	OCD+threat > neutral	√	√	√
Seoul, Korea (52)	Memory task with emotional distractor images	16	19	Images	–	Scenes	Scrambled	2.5	Threat > neutral	√	–	–
Shanghai, China	Aversive processing	27	29	Images	–	Scenes	Scrambled	1	Threat > neutral	√	–	–
Vancouver, Canada (53)	Symptom provocation	27	22	Images	Wash, order, bad thoughts/ sexual	Scenes	Scenes	4	OCD+threat > neutral	√	√	√

√ indicates that the contrast of interest was available in the sample's task data.
HC, healthy control participant; OCD, obsessive-compulsive disorder.

First-Level Contrast Parameter Estimate Maps. The guiding principle in creating first-level contrasts was to capture any form of negative valence (either OCD specific or generally threatening) and contrast this with processing of neutral stimuli (Table 1). In this way, we isolated negative valence processing across tasks regardless of which conditions existed across different tasks. Therefore, our main contrast of interest across all tasks was negative (OCD specific and/or threat) > neutral (n = 1086). In a subset of tasks where it was possible to do so, we also investigated the contrast threat > neutral (n = 1036) and the contrasts OCD > neutral (n = 606) and OCD > threat (n = 556) in symptom provocation tasks.

Participants were excluded if mean root mean square framewise displacement exceeded 0.5 mm. Each site also performed a quality assessment of its own data according to harmonized guidelines (see the Supplement) to verify, among other things, adequate signal-to-noise ratio in the functional image and accurate skull stripping, spatial normalization, and ICA-based artifact removal.

Analyses

Hypotheses and analyses were preregistered at the Open Science Framework (https://osf.io/7b4qz), but slight deviations were necessary in the analyses, as explained in Supplemental Methods.

Region-of-Interest Analyses. We investigated the bilateral regions of interest (ROIs) identified in Thorsen *et al.*'s (3) meta-analysis of negative valence processing: the amygdala, putamen, sgACC, vmPFC, LOC, and MTG. Cortical ROIs were created using a 5-mm sphere around coordinates of peak activation identified in Thorsen *et al.* (see Supplemental Methods) and warped to MNI152 NLIN 2009c (asymmetrical) space. Subcortical ROIs (amygdala, putamen) were taken from the Melbourne subcortical atlas scale 2 (15) rather than from published coordinates to preserve the anatomical and functional boundaries of these ROIs.

We extracted the mean activation of all voxels within an ROI from the z-statistic maps of each participant's first-level contrasts, which provided at least 30% of the voxels in the ROI-contained signal. Rather than applying separate general linear models to each ROI, we fed all regions into one Bayesian multilevel model (Region-based analysis [RBA], version 1.0.10) (16) that considered the shared nonindependent information across brain regions (derived from the same brain) in one model. Unlike the frequentist inference approach of quantifying the probability of the data given the hypothesis, Bayesian multilevel analysis allows us to quantify the evidence in favor of a particular hypothesis given the data. Therefore, we were able to combine a limited prior expectation (a noninformative Gaussian prior estimated from the data that minimally influence the conclusion) with the observed regional brain activations to obtain a measure of probability (the positive posterior distribution, summarized as P+ value) of our hypothesis, i.e., that brain activations differ between individuals with OCD and HCs. Advantages of this approach are that it captures the complex dependencies in the data (i.e., task activation of brain regions is nonindependent), dissolves the multiple testing problem, better controls for magnitude and sign errors, and crucially—unlike null hypothesis significance testing—it allows us to directly test the credibility of our hypotheses by outputting positive posterior distributions. This also stimulates full and transparent reporting of the results and eliminates pass/fail dichotomization based on (arbitrary) p values.

Nevertheless, for legibility, the posterior distributions are interpreted in the main text through the area under the curve to the right of the zero line, taking a positive posterior probability (P+) of <0.10 or >0.90 as indication of moderate evidence and <0.05 or >0.95 or <0.025 or >0.975 as strong or very strong evidence, respectively [cf. (17–19)]. We ran 4 Markov chains with 4000 permutations per chain, confirming model convergence by the statistic Rhat < 1.1 for all models.

Our main effect of interest was the case-control effect, with additional analyses for associations with clinical features. The effect of age of OCD onset was investigated by pairwise comparisons of adults with early-onset OCD (age of onset < 18), late-onset OCD (age of onset ≥ 18), and adult HCs. For all other analyses, children (age < 18) and adults (age ≥ 18) were grouped together. The effect of current medication status was investigated by pairwise comparisons of medicated individuals, unmedicated individuals, and HCs. The effect of OCD severity was assessed using (C)Y-BOCS scores as a continuous covariate. Age and sex at birth were entered as covariates of no interest in each Bayesian multilevel analysis. To control for potential confounding effects, sample (not site/institute because some sites contributed more than one sample) was also entered as a covariate of no interest. Multilevel Bayesian models like the one used in this analysis, when modeling sample/site, have been shown to outperform other common site correction strategies such as ComBat (20).

To further determine the robustness of these results, leave-one-sample-out sensitivity analysis was performed on the negative > neutral and threat > neutral contrasts for each ROI analysis. No leave-one-sample-out analysis was performed on the OCD > neutral and OCD > threat contrasts because they already represented a subsample of all tasks, namely symptom provocation tasks in which an OCD-relevant stimulus was presented. These contrasts constituted a sensitivity analysis for robustness to task effects because symptom provocation tasks made up the largest subset of negative valence tasks.

Whole-Brain Analyses. Because of large differences in brain coverage across participants, whole-brain analyses were done in larger functionally defined anatomical parcellations rather than voxelwise. z-statistic maps of each participant's first-level contrasts were parcellated using the Schaefer-Yeo 7-network 200-parcel atlas (21). Contrast estimates in each parcel were entered into identical Bayesian multilevel group analyses as detailed above. In addition, for proof of concept, we used an intercept model that pooled individuals with OCD and HCs during negative (OCD specific and/or threat) > neutral processing to infer a main effect of negative valence across all the different tasks. Sample, sex, and age were entered again as covariates of no interest.

RESULTS

Participants

After quality assessment, our final sample included 633 participants with OCD and 453 HCs (Table 2; Tables S1 and S3).

Table 2. Demographic Characteristics of the Total Sample

	OCD, n = 633	HC, n = 453	Statistic	p Value
Sex				
Female	333 (52.61%)	229 (50.55%)	$\chi^2_1 = 0.37$	.54
Male	300 (47.39%)	224 (49.45%)		
Age, Years	30.55 (11.21)	29.61 (11.74)	$t_{1084} = -1.33$	.18
< 18	55 (8.69%)	53 (11.7%)		
≥ 18	578 (91.31%)	400 (88.3%)		
Age of Onset, Years				
Onset < 18	316 (49.92%)	–	–	
Onset ≥ 18	212 (33.49%)	–	–	
Missing data	105 (16.59%)	–	–	
Medication Status				
Medicated	387 (61.14%)	–	–	
Unmedicated	245 (38.7%)	–	–	
Missing data	1 (0.16%)	–	–	
(C)Y-BOCS	23.9 (6.82)	–	–	
Missing data	7 (1.11%)	–	–	

Data are expressed as n (%) or mean (SD). Medication status refers to current medication status at time of scan.
(C)Y-BOCS, (Children's) Yale-Brown Obsessive Compulsive Scale; HC, healthy control participant; OCD, obsessive-compulsive disorder.

Proof of Concept: Negative Valence Contrast

We compared activation to all types of negatively valenced stimuli with all neutral stimuli across individuals with OCD and HCs (Figure 1). Very strong evidence of stronger activation in response to negative (vs. neutral) stimuli emerged in multiple prefrontal, limbic, and occipital regions in whole-brain analyses, which was not driven by any particular task type (Figure S2). Weaker activation was seen in sensorimotor regions. ROI analyses revealed very strong evidence of weaker bilateral sgACC activation during negative versus neutral processing and stronger activation in all other regions (Figure S1).

Negative Valence in the OCD Versus the HC Group

In ROI analyses, individuals with OCD (compared with HCs) showed very strong evidence of weaker activation in the bilateral LOC (P+ < 0.001) and moderate evidence of stronger activation in the bilateral sgACC (left P+ = 0.94, right P+ = 0.92) and right vmPFC (P+ = 0.90) (Figure 2B). This hyperactivation to negative stimuli in frontal regions was driven by generally threatening stimuli (moderate evidence; left sgACC P+ = 0.92, right vmPFC P+ = 0.95) and not OCD-specific stimuli.

Whole-brain analyses confirmed that during negative valence processing, individuals with OCD showed weaker activation than HCs in the entire visual cortex and frontoparietal areas, as well as the posterior thalamus (Figure 2C). Activation of inferior somatomotor regions and upper medial temporal regions was stronger in OCD during the negative versus the neutral valence condition. This pattern of stronger and weaker activation was broadly similar for OCD-specific (vs. neutral) and generally threatening (vs. neutral) stimuli. However, when comparing OCD-specific versus threat stimuli in the symptom provocation tasks (8 samples), we observed credible evidence for stronger activation in OCD throughout the prefrontal cortex, visual areas, cingulate cortex, inferior parietal regions, bilateral caudate, bilateral anterior putamen, and right posterior thalamus (all P+s > 0.9) during OCD-specific negative valence processing.

Clinical Features: OCD Onset, Medication, and Symptom Severity

Age of Onset. Adults with late-onset (vs. early-onset) OCD showed moderate to very strong evidence of stronger activation during the negative (vs. neutral) valence condition in all prefrontal ROIs (P+ > 0.91) and the right MTG (P+ = 0.93)

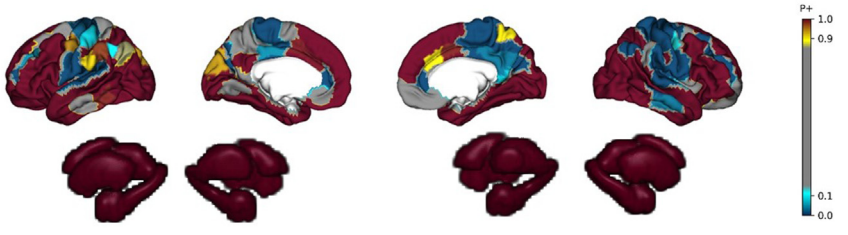

Figure 1. Main effect of negative valence. Whole-brain analysis of group-level negative (obsessive-compulsive disorder [OCD] specific and/or threat) > neutral contrast across individuals with OCD and healthy control participants (n = 1086). Regions are color coded to reflect the strength of evidence for an effect; in (darker) red regions, there is stronger evidence of activation while viewing negatively valenced stimuli than neutral stimuli (P+ values > 0.90 indicate moderate to very strong evidence for a positive effect). In (darker) blue regions, there is stronger evidence of deactivation during negatively valenced stimuli than neutral stimuli (P+ values < 0.10 indicate moderate to very strong evidence for a negative effect). In gray regions, there is no strong evidence of activation or deactivation to negatively valenced stimuli compared with neutral stimuli. Lateral and medial views of the left and right cortex (upper panel) and subcortex (lower panel) are visible.

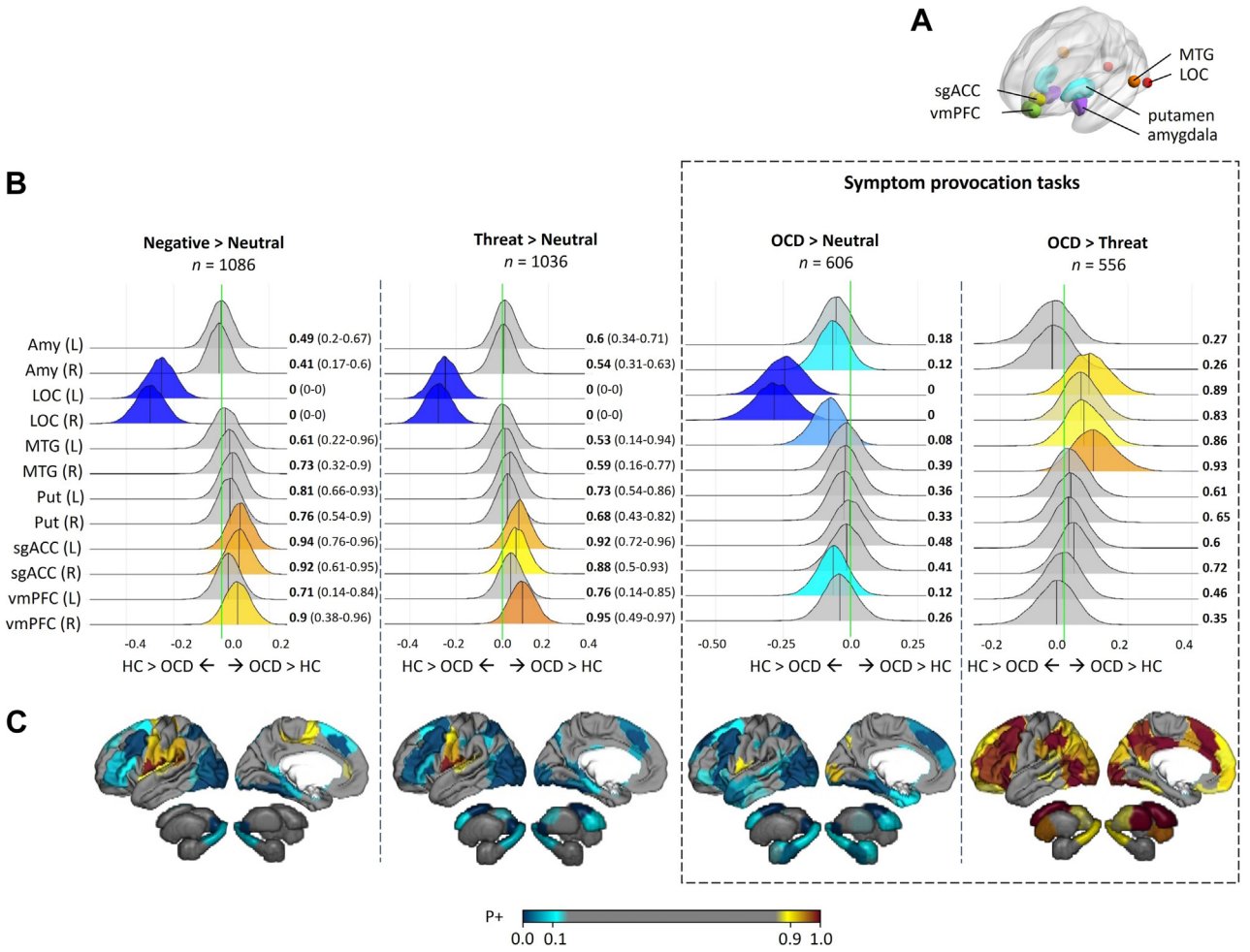

Figure 2. Case-control differences in negative valence processing. **(A)** Regions that were investigated based on the meta-analysis of Thorsen *et al.* (3). **(B)** Region-of-interest effects from Bayesian multilevel analyses. Posterior probability distributions expressing the credibility of an effect in each region are visualized. Next to each distribution, the posterior probability of a positive effect (P+) is shown in bold, as well as the range of values that this probability took on in leave-one-sample-out sensitivity analyses (for the contrasts where this analysis was carried out). Distributions to the right of the green no-effect line represent regions in which individuals with obsessive-compulsive disorder (OCD) show evidence for higher activation than healthy control participants (HCs). Regions with posterior distributions to the left of this line show evidence for higher activity in HCs than in individuals with OCD. Distributions are color coded to reflect the strength of evidence for an effect, where (darker) red color represents regions in which individuals with OCD show moderate-to-very-strong evidence for higher activation than HCs. (Darker) blue color represents regions in which HCs show moderate-to-very-strong evidence for higher activation than individuals with OCD. Gray color represents regions in which there is no evidence of a difference between HCs and individuals with OCD. Values on the x-axis represent the difference in regional activation levels between HCs and individuals with OCD (expressed as difference in *z* scores). **(C)** Whole-brain effects from Bayesian multilevel analyses. P+ values derived from Bayesian multilevel analyses denote the probability that there is increased brain activation in a given region of the Schaefer-Yeo 7-network 200-parcel cortical atlas and Melbourne 32-region subcortical atlas. Displayed are lateral and medial views of only the left hemisphere's cortex (upper panel) and subcortex (lower panel) because results were largely symmetrical, but bilateral results are shown in Figure S3. Amy, amygdala; L, left; LOC, lateral occipital cortex; MTG, medial temporal gyrus; Put, putamen; R, right; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.

(Figure 3A). Both onset groups showed strong evidence for weaker activation of the bilateral LOC than HCs ($P+ < 0.001$), but late-onset OCD individuals showed even weaker activity than early-onset individuals (left $P+ = 0.05$, right $P+ = 0.02$) (Figure S4). Whole-brain analyses did not yield credible evidence for any differences between the onset groups (Figure 3B).

Medication Status. In ROI analyses, medicated individuals with OCD showed weaker activation of the left MTG (moderate evidence, $P+ = 0.03$) and stronger activation of the right LOC (moderate evidence, $P+ = 0.93$) during the negative (vs. neutral) valence condition than unmedicated individuals (Figure 3A). During OCD-specific versus neutral processing, medicated individuals showed very strong evidence of stronger bilateral LOC activation ($P+ > 0.999$) relative to their unmedicated counterparts (Figure S6), although both groups showed very strong evidence of weaker activation than HCs ($P+ < 0.001$). In whole-brain analyses, medicated individuals

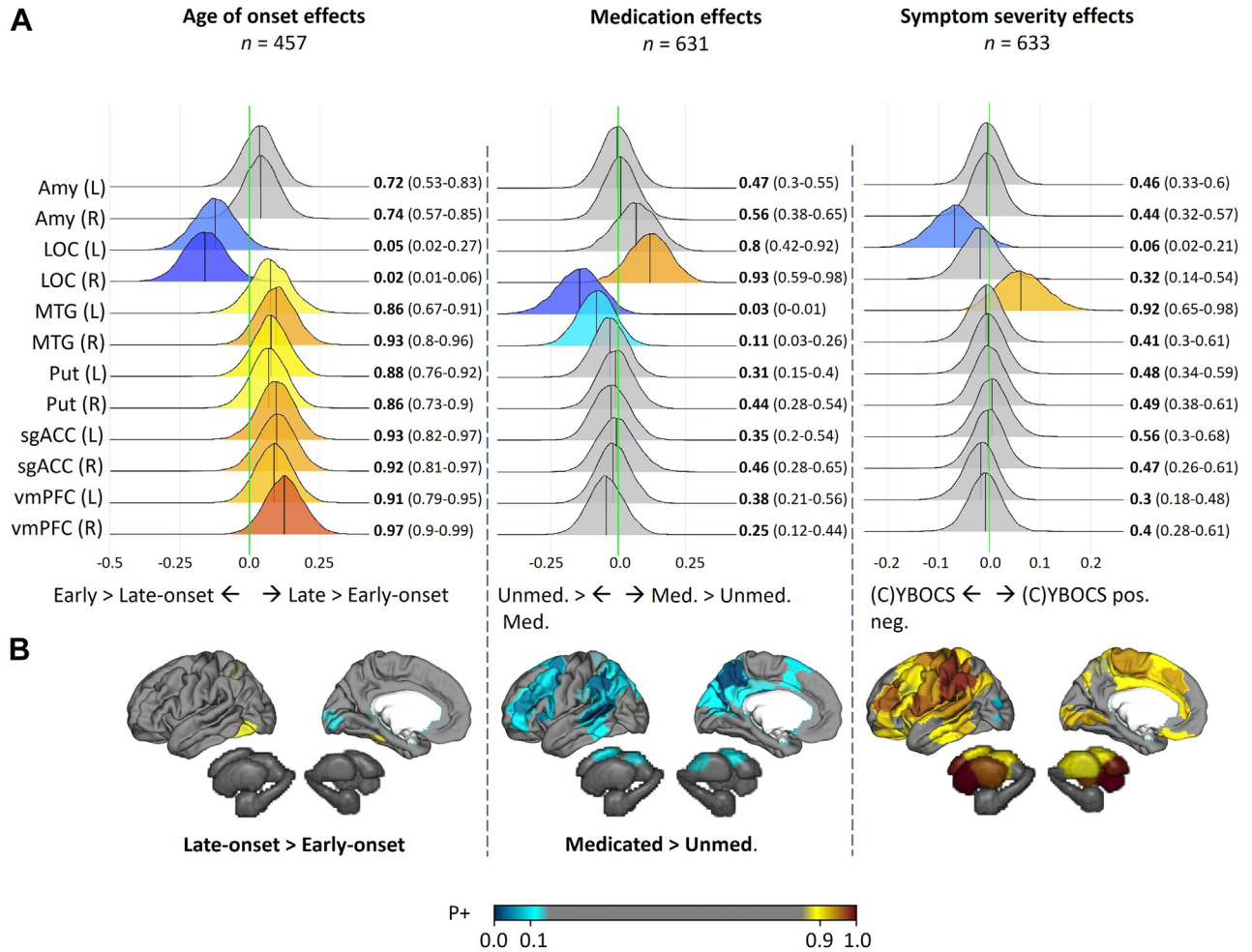

Figure 3. Effects of clinical features on negative valence processing. **(A)** Region-of-interest effects of age of onset, medication status, and symptom severity during negative (obsessive-compulsive disorder [OCD] specific and/or threat) > neutral processing. **(B)** Whole-brain analyses of negative (OCD specific and/or threat) > neutral processing, displaying only left hemisphere results (bilateral results are shown in Figures S5, S7, and S9). Amy, amygdala; (C)Y-BOCS, (Children's) Yale-Brown Obsessive Compulsive Scale; L, left; LOC, lateral occipital cortex; Med., medication; MTG, medial temporal gyrus; neg., negative; pos., positive; Put, putamen; R, right; sgACC, subgenual anterior cingulate cortex; Unmed., unmedicated; vmPFC, ventromedial prefrontal cortex.

exhibited weaker activation than unmedicated individuals during negative valence processing in inferior parietal, precuneus, and lateral prefrontal regions, as well as the posterior caudate and anterior thalamus (Figure 3B). This was more pronounced for generally threatening stimuli than for OCD-specific stimuli, with credible evidence for a difference in prefrontal activation between medication groups only for threat stimuli. Medicated individuals drove the stronger activation in symptom provocation tasks to OCD-specific versus threat stimuli seen in prefrontal, visual, cingulate, and parietal areas (Figure S7).

Symptom Severity. During the negative (vs. neutral) valence condition, ROI analyses showed moderate evidence for a positive association of OCD severity with activity in the left MTG (P+ = 0.92) and a negative association with activity in the left LOC (P+ = 0.06) (Figure 3A). Whole-brain analyses showed that OCD severity was associated with stronger activation during the negative (vs. neutral) valence condition in prefrontal, inferior parietal, and temporal regions, as well as in the putamen and anterior caudate nucleus (Figure 3B).

Robustness of Findings

Using leave-one-sample-out sensitivity analyses, we observed high consistency of the results in the lateral occipital regions (Figure S11). We saw robust findings in other regions when we compared individuals with early- versus late-onset OCD and when associating activation with symptom severity. Results were more robust for comparisons of unmedicated individuals with OCD to either medicated individuals or HCs than for comparisons of medicated individuals to HCs. The consistency of the results was reduced when we left out any of the 3 largest samples ($n > 124$).

DISCUSSION

This study represents the first worldwide investigation that used individual whole-brain statistical maps derived from

different negative valence paradigms to perform a mega-analysis in OCD. Across tasks and groups, we showed a single common activation pattern that included activation in frontolimbic and lateral occipital regions that are central to negative valence (vs. neutral) processing (22). Compared with HCs, individuals with OCD showed robust and highly credible evidence of weaker activation of the LOC and adjacent visual processing regions, which were observed equally for OCD-specific and generally threatening (vs. neutral) stimuli. This activation was related to the late onset of OCD, unmedicated status, and greater symptom severity. Individuals with OCD also showed stronger activation in ventral prefrontal regions, i.e., the OFC, sgACC, and vmPFC. Stronger prefrontal activation was mainly observed with generally threatening, not OCD-specific stimuli, and was more pronounced in late-onset OCD and more severe OCD.

Our results may indicate that individuals with OCD process negatively valenced visual information differently than HCs beginning already at the very early stages of image processing and visual integration. The regions involved here were highlighted by two previous coordinate-based meta-analyses, although Thorsen *et al.* (3) reported stronger activation, while Yu *et al.* (4) reported weaker activation in individuals with OCD. The ENIGMA Consortium also previously observed lower left LOC cortical thickness in children with OCD (23) and lower local resting-state activity and global connectivity in multiple occipital cortex regions (24), suggesting that visual areas show OCD-related dysfunction across imaging modalities. In support of this idea, in an independent dataset, the investigators found lower surface area of the right occipital lingual gyrus in unmedicated adults with OCD than HCs (25). Occipital cortex hypoactivation has also been seen in attention-deficit/hyperactivity disorder during a distraction task (26) and in major depressive disorder during a negatively valenced task (27). A deficit in early visual processing in OCD has long been posited (28) and has recently been supported by electroencephalographic evidence of potentiated responses of early visual areas to neutral stimuli (29) and biased attention for ambiguous stimuli, even when they are neutral (30). Considering the greater ambiguity in neutral conditions in the tasks used here, this may explain the stronger occipital activation that we found in neutral than negative valence processing in OCD. To the extent that individuals with OCD may have diverted attention or even gaze from unpleasant stimuli in these tasks, the stronger activation of the LOC for OCD-specific stimuli than for generally threatening stimuli may reflect an inherent vigilance for disorder-relevant information. This is further supported by findings of increased activation of the occipital lobe across 4 anxiety-related disorders during disorder-relevant image viewing (31). Altered sensory processing may explain this, such that when negatively valenced stimuli are disorder relevant, the flexibility of attentional allocation is reduced. Studies with varying visual complexity of neutral and emotional information, complemented with eye tracking, are needed to spatially localize where in the fronto-occipital cortices OCD differences reside and which attentional processes they affect.

We found evidence of stronger OCD-related activation of orbitofrontal and anterior cingulate regions during negative valence processing, consistent with Thorsen *et al.* (3). Orbitofrontal regions may be hyperactivated by the salience of negatively valenced stimuli (32), leading these regions to exert aberrant inhibitory control on the visual cortex. This in turn may impair bottom-up attention processes, allocating cognitive resources to threat and vigilance systems at the expense of deeper processing and contextualization of visual information. Prefrontal hyperactivation has been proposed to be a compensatory mechanism in OCD that boosts cognitive control to override limbic or striatal interference and guide behavior (33,34). The activation of limbic and striatal regions seen in our task effects would support a compensatory function of prefrontal activation. However, this prefrontal activation was sensitive to individual differences in clinical features and specific task contrasts and appeared to be highly localized because it was not replicated at the coarser whole-brain level. Individuals with late-onset OCD had stronger prefrontal activation and greater deviation from control individuals, which, contrary to our predictions, does not indicate a more chronic developmental trajectory for early-onset OCD. We also found evidence of stronger MTG activation in unmedicated than medicated individuals and in individuals with more severe symptoms, indicating sensitivity of corticolimbic regions to symptom states.

Unexpectedly, we did not find evidence of stronger amygdala activation in negative valence processing in OCD, although the main effect of negative valence demonstrated that the amygdala was strongly activated in both groups. Based on the dual-pathway theory of threat processing, visual information is passed along either the direct route from the retina via the pulvinar thalamus to the amygdala (quick and dirty processing) or along the indirect route from the (visual) cortex via the geniculate thalamus, arriving highly elaborated to the amygdala (35,36). While we did not observe amygdala activation differences between individuals with OCD and HCs, we did observe increased activation of the posterior ventral thalamus, which overlaps with the pulvinar, in OCD. This, combined with the stronger prefrontal cortical activity and weaker occipital cortical activity that we observed in OCD, may indicate dysfunction in the inputs to the amygdala. A contemporary view of the amygdala's role in emotion processing is to coordinate the function of cortical networks to evaluate an affective valence (37), and our results indicate that the inputs from both the direct and the indirect pathway may be disturbed in OCD. Future task designs could contrast subliminal with supraliminal aversive stimuli to distinguish OCD-related dysfunction in these pathways while temporally characterizing their interaction with the amygdala.

Currently, first-line therapies for OCD mainly focus on retraining excessive emotional responses to the stimuli that provoke obsessions and/or compulsions (38), although our findings suggest that treatments should not ignore the role of bottom-up visual attention processing across stimulus valences. Antidepressant medication did appear to boost LOC activation and normalize some cortical hyperactivation in individuals with OCD, but selectively for generally threatening stimuli and not for OCD-specific stimuli, which could explain why it has limited success in treating OCD (39,40). A recent study found differing effects of treatment with antidepressants versus cognitive behavioral therapy for OCD in the occipital cortex and particularly in the white matter of the ventral visual

stream following a symptom provocation task (41). If distinct pathways are implicated in treatment response for OCD, it is relevant to examine which of these pathways has the ability to address the bottom-up visual impairments seen here, possibly through compensatory prefrontal cognitive control. Although this has not been tested yet in OCD, studies with both HCs (42) and clinical populations such as stroke survivors (43) support the possibility of boosting visual cortex activation through cognitive training or biofeedback.

One of the inherent limitations of consortia like ENIGMA that work with retrospective legacy data is the lack of harmonized data collection and reporting of information across samples. We lacked detailed information about, among others, dose, duration, and type of pharmacotherapy or current non-pharmacological therapies, comorbid disorders, exact age of OCD onset, and OCD symptom subtypes. Task designs were not harmonized and likely captured slightly different cognitive processes across task conditions. This was further exacerbated by variations in the neutral condition across tasks because some tasks used scenes while others used scrambled images. Nonetheless, the effects observed in the LOC were extremely robust to leave-one-sample-out sensitivity analyses. Across analyses in other ROIs, we found no consistent effects of task characteristics (i.e., task paradigm, type of stimuli), although clinical features appeared to be a source of variance in medication and chronicity effects. This underscores the importance of pooling participant-level data to accurately capture the heterogeneity of OCD. A direct comparison of coordinate-based and image-based meta-analysis on the same set of datasets found that even the best-performing coordinate-based meta-analytic method conferred a Dice similarity coefficient of only 0.45 (on a scale of 0–1) to the image-based gold-standard method (44), indicating a substantial loss of sensitivity. Given our access to both participant-level whole-brain contrast maps and clinical data, we believe that our analyses were better powered to detect true effects than previous meta-analyses. We consider the strong task effect as evidence of a common negative valence circuit that lends itself to studying task-independent emotional dysfunction in a larger and more heterogeneous sample than ever before. The Bayesian analytic framework allowed us to report richer effect estimates, identify regions in which there is no evidence of difference, and afford greater confidence in the strength of the observed effects.

Conclusions

Our analyses indicate that people with OCD have highly localized alterations in negative valence processing in prefrontal regions and show general deficits in visual processing regions. Results in the prefrontal cortex were shown to be sensitive to particular task contrasts, medication usage, age of onset, and OCD severity, supporting the application of data merging in large mega-analyses to model medication and disorder-induced effects with adequate power.

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ARTICLE INFORMATION

From the Department of Anatomy & Neurosciences, Amsterdam University Medical Center, Amsterdam, the Netherlands (ND, CV, AB, SMDDF, NTdJ, TSP, YDvdW, OAvdH); Department of Psychiatry, Amsterdam University Medical Center, Amsterdam, the Netherlands (ND, CV, AB, DD SMDDF, NTdJ, WvL, HJFvH, TSP, ALvdS, DJV, HV, YDvdW, GvW, OAvdH); Amsterdam Neuroscience, Amsterdam University Medical Center, Amsterdam, the Netherlands (ND, CV, AB, DD SMDDF, NTdJ, WvL, HJFvH, TSP, ALvdS, DJV, GvW, OAvdH); Compulsivity, Impulsivity and Attention, Amsterdam University Medical Center, Amsterdam, the Netherlands (ND, CV, AB SMDDF, NTdJ, TSP, DJV, IMV, OAvdH); Department of Psychiatry and Neurosciences, Charité Campus Mitte, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany (LW, SE, HW); Columbia University Irving Medical College, Columbia University, New York, New York (HBS); Center for Obsessive-Compulsive Disorder and Related Disorders, New York State Psychiatric Institute, New York, New York (HBS); Icahn School of Medicine at Mount Sinai, New York, New York (II); Department of Psychiatry, Obsessive-Compulsive Disorder Clinic, National Institute of Mental Health and Neurosciences, Bangalore, India (SMA, SB, JCN, VS); Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (SMA); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (SMA); Department of Psychiatry, The Institute of Biomedical Research of Bellvitge, Barcelona, Spain (PA, IM-Z, JMM, CS-M); Department of Clinical Sciences, Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain (PA, JMM); Centro de Investigación Biomédica En Red de Salud Mental, Carlos III Health Institute, Madrid, Spain (PA, JMM, CS-M); Department of Child and Adolescent Psychiatry, Faculty of Medicine of the Technische Universität Dresden, Dresden, Germany (LLB. VR, NCV); Mental Healthcare Institute Geestelijke Gezondheidszorg Centraal, Amersfoort, the Netherlands (AB); Coimbra Institute for Biomedical

Imaging and Translational Research, Instituto de Ciências Nucleares Aplicadas à Saúde, University of Coimbra, Coimbra, Portugal (MC-B, ICD); Faculty of Medicine, University of Coimbra, Coimbra, Portugal (MC-B); Life and Health Sciences Research Institute, School of Medicine, University of Minho, Braga, Portugal (ADC, PM, MP-P); Clinical Academic Center of Braga, Braga, Portugal (ADC, PM); Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom (HC, VV); Department of Psychiatry, New York University Grossman School of Medicine, New York, New York (GKE, ERS; Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York (GKE, ERS); Department of Psychiatry and Mental Health, Brain Behaviour Unit, University of Cape Town, Cape Town, South Africa (JI, ISO); Neuroscience Institute, University of Cape Town, Cape Town, South Africa (JI, ISO, DJS); Department of Psychiatry, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada (FJ-F, SES); British Columbia Children's Hospital Research Institute, Vancouver, British Columbia, Canada (FJ-F, SES); Department of Psychiatry, Seoul National University College of Medicine, Seoul, South Korea (MK, JSK); Department of Neuropsychiatry, Seoul National University Hospital, Seoul, South Korea (MK, JSK); Department of Diagnostic and Interventional Neuroradiology, School of Medicine, Technical University of Munich, Munich, Germany (KK, DR-M); Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, Seoul, South Korea (JSK); Arkin Mental Health Care, Amsterdam, the Netherlands (WvL); South African Medical Research Council Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry, Stellenbosch University, Stellenbosch, South Africa (CL, DJS); Mental Healthcare Institute Geestelijke Gezondheidszorg inGeest Mental Health Care, Amsterdam, the Netherlands (HJFvH, TSP); Department of Radiology, Hospital Universitari de Bellvitge, Barcelona, Spain (IM-Z); Faculty of Health, School of Medicine, Deakin University, Geelong, Victoria, Australia (JCN); Goulburn Valley Health, Shepparton, Victoria, Australia (JCN); Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Castellón de la Plana, Spain (MP-P); Department of Clinical Psychology, Leiden University, Leiden, the Netherlands (OGR-O); Department of Social Psychology and Quantitative Psychology, Institute of Neurociences, University of Barcelona, Barcelona, Spain (CS-M); Neuroscience Institute, New York University Grossman School of Medicine, New York, New York (ERS); Levvel, Academic Center for Child and Adolescent Psychiatry and Specialized Youth Care, Amsterdam, the Netherland (ALvdS); Department of Neurosurgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (BS); Center for Functional Neurosurgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (BS); Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of the University of Southern California, Marina del Rey, California (SIT, PMT); Department of Psychology, Medical School Berlin, Berlin, Germany (NCV); Fudan University, Shanghai, China (VV); Department of Developmental Psychology, University of Amsterdam, Amsterdam, the Netherlands (IMV).

ENIGMA-OCD Working Group members: Sara Bertolin, M.D. (1,2,3), Nicole Beyer, Ph.D. (4), Joao Castelhano, Ph.D. (5), Sunah Choi, B.S. (6), Beatriz Couto, M.D. (7), Eva Real, M.D., Ph.D. (1,3), Cinto Segalas, M.D., Ph.D. (1,3), Nuno Sousa, M.D., Ph.D. (7,8), Anne Uhlmann, Ph.D. (4), and Yijie Zhao, Ph.D. (9,10)

(1) Department of Psychiatry, The Institute of Biomedical Research of Bellvitge, Barcelona, Spain; (2) Department of Clinical Sciences, Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain; (3) Centro de Investigación Biomédica En Red de Salud Mental, Carlos III Health Institute, Madrid, Spain; (4) Department of Child and Adolescent Psychiatry, Faculty of Medicine of the Technische Universität Dresden, Dresden, Germany; (5) Coimbra Institute for Biomedical Imaging and Translational Research, Instituto de Ciências Nucleares Aplicadas à Saúde, University of Coimbra, Coimbra, Portugal; (6) Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, Seoul, South Korea; (7) Life and Health Sciences Research Institute, School of Medicine, University of Minho, Braga, Portugal; (8) Clinical Academic Center of Braga, Braga, Portugal; (9) Shanghai Pudong New Area Mental Health Center, School of Medicine, Tongji University, Shanghai, China; (10) Fudan University, Shanghai, China.

IMV and OAvdH are joint last authors.

Address correspondence to Nadza Dzinalija, M.Sc., at n.dzinalija@amsterdamumc.nl.

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