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REVIEW ARTICLE

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An overview of the first 5 years of the ENIGMA obsessive–compulsive disorder working group: The power of worldwide collaboration

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Abstract

Neuroimaging has played an important part in advancing our understanding of the neurobiology of obsessive–compulsive disorder (OCD). At the same time, neuroimaging studies of OCD have had notable limitations, including reliance on relatively small samples. International collaborative efforts to increase statistical power by combining samples from across sites have been bolstered by the ENIGMA consortium; this provides specific technical expertise for conducting multi-site analyses, as well as access to a collaborative community of neuroimaging scientists. In this article, we outline the background to, development of, and initial findings from ENIGMA's OCD working group, which currently consists of 47 samples from 34 institutes in 15 countries on 5 continents, with a total sample of 2,323 OCD patients and 2,325 healthy controls. Initial work has focused on studies of cortical thickness and subcortical volumes, structural connectivity, and brain lateralization in children, adolescents and adults with OCD, also including the study on the commonalities and distinctions across different neurodevelopment disorders. Additional work is ongoing, employing machine learning techniques. Findings to date have contributed to the development of neurobiological models of OCD, have provided an important model of global scientific collaboration, and have had a number of clinical implications. Importantly, our work has shed new light on questions about whether structural and functional alterations found in OCD reflect neurodevelopmental changes, effects of the disease process, or medication impacts. We conclude with a summary of ongoing work by ENIGMA-OCD, and a consideration of future directions for neuroimaging research on OCD within and beyond ENIGMA.

KEYWORDS
cortical thickness, ENIGMA, mega-analysis, meta-analysis, MRI, obsessive–compulsive disorder, surface area, volume

1 | BACKGROUND

Since the 1980s, obsessive–compulsive disorder (OCD) researchers worldwide have made extensive use of neuroimaging (Behar et al., 1984; Luxenberg et al., 1988). OCD has a distinctive phenotype, with characteristic repetitive thoughts and intrusions (obsessions) and habitual behaviors (compulsions), and there was early evidence of the involvement of specific brain circuits and systems (Cummings, 1995). Early hypotheses regarding brain systems involved were based on clinical observations, including descriptions of OCD-like behaviors in patients with subcortical disorders, such as Huntington's disease (Cummings & Cunningham, 1992), Sydenham's chorea (Swedo, Rapoport, Cheslow, & Ayoub, 1989), and pallidal (Laplane et al., 1989) and frontal lobe (Eslinger & Damasio, 1985) lesions. Data obtained with human brain imaging in the late 1980s allowed detailed neurobiological models of OCD to be developed. These models initially focused on the striatum and orbitofrontal cortex, but were later refined to include more broadly interacting

fronto-striatal, fronto-parietal, fronto-limbic, and cerebellar circuits (Stein et al., 2019; Van den Heuvel et al., 2016).

The first brain imaging studies in OCD focused on brain morphometry and glucose metabolism, using computed tomography (CT) (e.g., Behar et al., 1984), single photon emission computed tomography (SPECT) and positron emission tomography (PET) (e.g., Rubin, Anath, Villanueva-Meyer, Trajmar, & Mena, 1995). In the 1990s, magnetic resonance imaging (MRI) began to dominate the field. High resolution structural MRI enabled morphometric analyses of subcortical volume and shape, cortical thickness and surface area, as well as cortical gyrification. Functional MRI (fMRI) began to be used to visualize brain activation patterns during specific states relevant to the disorder, using a range of emotional and cognitive paradigms that may be crucial in the disease, for example, symptom provocation (Jaspers-Fayer et al., 2019; Thorsen et al., 2018), fear and extinction learning (Milad et al., 2013), response inhibition (Norman et al., 2019), planning (e.g., Van den Heuvel et al., 2005), working memory (e.g., De Vries et al., 2014), and reversal learning (e.g., Remijnse et al., 2006).

In the past decade, imaging designs began to shift from analyzing specific regions of interest to studying whole-brain networks. Network approaches can be used to examine structural connectivity, using diffusion weighted imaging (DTI; Piras, Piras, Caltagirone, & Spalletta, 2013; Radua et al., 2014) as well as structural covariance (Yun et al., 2020), and functional connectivity at rest (Gursel, Avram, Sorg, Brandl, & Koch, 2018) and during task performance (e.g., Douw et al., 2019). As with other neuroimaging studies, a key challenge has been the reproducibility of research findings, as most single center imaging studies have limited statistical power to detect effects of the disorder, while adequately controlling for multiple comparisons and heterogeneity in demographic and clinical characteristics. Although each individual study differs in the choice of paradigms, a structural MRI scan is typically part of every study design, enabling meta-analyses of data across many samples, or mega-analyses of pooled raw MRI scans or MRI-extracted measures. Although technically more challenging, meta-analyses and mega-analyses of resting state fMRI (rsfMRI), and even task-based fMRI, are also possible (Adhikari et al., 2018; Adhikari et al., 2019; Yan et al., 2019).

1.1 | The first worldwide data-sharing initiative: The OCD brain imaging consortium

The first large single-center structural MRI study of OCD was published in 2004 by Pujol et al., based on MRI scans of 72 OCD patients and 72 controls, using voxel-based morphometry (VBM) (Ashburner & Friston, 2000; Pujol et al., 2004). Compared to healthy controls, OCD patients had, on average, smaller volumes for the medial frontal gyrus, medial orbitofrontal cortex and left insula-operculum, and greater volumes for the ventral part of the putamen and anterior cerebellum. The striatal finding was mainly driven by older patients and those with longer disease duration. Pujol et al. (2004) also found that although these frontal-striatal abnormalities were present across the various subtypes of OCD, specific phenotypes showed additional neural alterations: aggressive obsessions and checking compulsions were associated with smaller right amygdala. Subsequently, these effects were largely replicated by the symptom dimension findings of Van den Heuvel et al. (2009).

Multiple conventional meta-analyses of VBM studies of OCD were subsequently published (Radua & Mataix-Cols, 2009; Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010; Rotge et al., 2010; Peng et al., 2012), using statistical methods to aggregate information on effect sizes, standard errors, and confidence intervals from primary published studies, in order to estimate overall effect size. To meta-analyze voxel-based data, an often-used approach is the signed differential mapping (SDM) method, developed by Radua (https://www.sdmproject.com). A meta-analysis using this method showed that compared to healthy controls, OCD patients have, on average, lower volumes of the dorsomedial prefrontal cortex (dmPFC)/dorsal anterior cingulate cortex (dACC) and greater volume of the bilateral striatum (mainly anterior putamen, extending into the caudate nucleus) (Radua & Mataix-Cols, 2009). In comparison to other anxiety disorders, smaller volume of the dmPFC/dACC was found across disorders, whereas OCD patients had greater pallidal volume than did patients with anxiety disorders (Radua et al., 2010). An even larger cross-disorder meta-analysis of brain volume across mental disorders, including 193 studies (15,892 subjects) in six diagnostic groups (schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, OCD, and anxiety disorders) showed that smaller volume of the dACC and bilateral insula/operculum was not specific to OCD, but was consistently present across all these psychiatric disorders (Goodkind et al., 2015).

These aggregate meta-analyses, based on published data, were highly informative, but still prone to publication bias, selective reporting in primary studies, large variations in data processing and analyses across studies influencing the results, and insufficient power to undertake detailed investigations of the associations between clinical characteristics and neuroimaging findings (Boedhoe et al., 2019). To address these limitations, the OCD Brain Imaging Consortium (OBIC) was initiated in 2010; this initiative aimed to increase statistical power by pooling raw MRI data from centers around the world. Harmonization of data quality control and data processing, all performed at a single center, would limit variation across data samples to just the variation in inclusion criteria and data acquisition. Six academic OCD centers (from Asia, Europe, and South America) provided high-quality data from 412 adult OCD patients and 368 healthy controls. Using VBM, the OBIC consortium mega-analysis showed that compared to healthy controls, OCD patients had lower volume of the dmPFC, dACC, and bilateral insula-operculum, largely replicating previous meta-analytic findings (Goodkind et al., 2015; Radua et al., 2010; Radua & Mataix-Cols, 2009), as well as greater volume of the cerebellum. Group-by-age interaction effects illustrated that some regions (e.g., putamen) show a relative preservation of volume in OCD with increasing age while other regions (e.g., temporal regions) show a relative loss of volume in OCD with increasing age. These findings are consistent with the initial study by Pujol et al. (2004), and suggest that

increased volume of the striatum/pallidum is most prominent in older OCD patients, perhaps related to disease chronicity.

Using the same OBIC dataset, structural covariance analysis of four striatal regions and two amygdala regions was performed, showing increased covariance between the volume of the ventral-rostral putamen and the left inferior frontal gyrus/operculum. Consistent with the previous findings, this association was only significant in older OCD patients, suggesting that these alterations may develop over the course of the disease (Subira et al., 2016). In addition to this fronto-striatal finding, increased covariance was found between the right centromedial-superficial part of the amygdala and the ventromedial prefrontal cortex, consistent with the role of the limbic circuit in OCD, as evident in functional MRI studies on emotional processing in this disorder (Milad et al., 2013; Thorsen et al., 2018).

Whereas VBM measures volume or gray matter density in cortical regions at the voxel level (Ashburner & Friston, 2000), surface-based methods such as FreeSurfer calculate morphometric measures from geometric models of the cortical surface (Fischl & Dale, 2000). Abnormalities in regional volume as measured with VBM can be the result of altered cortical thickness (CTh), surface area (SA), cortical folding, or a combination of these. Whereas cortical thickness changes dynamically across the lifespan as a consequence of development, disease and environmental factors (Eyler et al., 2011; Frye et al., 2010), surface area and cortical folding are more indicative of early neurodevelopment (Mangin, Jouvent, & Cachia, 2010). Atlas-based approaches as used in FreeSurfer and voxel-based approaches as used in VBM also differ in their approach to and interpretation of subcortical regions: Whereas VBM detects density differences at the voxel-level, global or regional differences in subcortical structures can be inferred from atlas-based FreeSurfer analyses. Using exactly the same OBIC sample as was used in the VBM mega-analysis (De Wit et al., 2014), Fouche et al. (2017) used vertex-wise FreeSurfer to compare cortical thickness and subcortical volumes in patients versus controls, and showed that adult OCD patients have a thinner cortex in a number of frontal, temporal, and parietal regions and smaller bilateral hippocampus. These findings partly overlap with the VBM-based results, but also show that results and their interpretation depend to some extent on the methods used.

1.2 | Extension to children and better worldwide coverage: The ENIGMA-OCD consortium

In 2009, Paul Thompson initiated the ENIGMA (Enhancing Neuroimaging and Genetics through Meta-analysis) consortium. ENIGMA has now grown to a collaboration of more than 1,400 scientists from 43 countries studying the human brain, both in health and disease (Thompson et al., 2019). The initial aim was to perform large-scale neuroimaging genetics analyses, by pooling worldwide data, resources and expertise, to answer clinical and fundamental questions related to psychiatric and neurological disorders. The consortium currently has 30 working groups on specific psychiatric and neurological disorders, a few on trans-diagnostic constructs (e.g., irritability, suicidality, and lifespan), and 12 that develop and disseminate analysis pipelines, to facilitate harmonization across working groups.

With the goals of obtaining larger sample sizes than represented in OBIC, increasing worldwide coverage, extending the samples to pediatric OCD, comparing OCD to other disorders, and eventually combining imaging data and genetics, van den Heuvel and Stein proposed adding an ENIGMA-OCD working group to the ENIGMA consortium in 2013. As of 2019, ENIGMA-OCD consists of 47 samples from 34 institutes in 15 countries on 5 continents, with a total sample of 4,648 with MRI data of 2,323 OCD patients (1,824 adults (>18 years), 359 adolescents (12–17 years), 140 children (<12 years)) and 2,325 controls (1,724 adults, 325 adolescents, and 166 children; Figure 1).

The standard procedure in ENIGMA has been collation of individual-participant data (IPD; e.g., value of CTh, SA, subcortical volume, and intracranial volume) from multiple studies, without requiring the sharing or centralization of the raw MRI data, as was done in OBIC. The advantage of meta-analysis on IPD without the need to exchange raw data is of particular relevance in the context of the new European law, that is, the General Data Protection Regulation 2016/679, regulating data protection and privacy for all individual citizens of the European Union (https://gdpr-info.eu/). Using standardized protocols for data processing and quality control (see also: http://enigma.ini.usc.edu/protocols/), all data are processed at each site locally. Standardization of protocols, within working groups and across working groups, ensures low methodological heterogeneity across sites and working groups. IPD can subsequently be used in two different statistical approaches: A two-stage or a one-stage approach (Boedhoe et al., 2019). In the two-stage approach, IPD are first analyzed for each sample separately to obtain summary results (e.g., effect size estimates, confidence intervals, and so on), which are then used for standard meta-analysis. In contrast, the one-stage approach analyzes all IPD in one statistical model, while accounting for site effects, to estimate the overall effect. In the ENIGMA-OCD publications we call the two-stage approach *meta*-analysis, and the one-stage approach *mega*-analysis. Whereas in OBIC we conducted mega-analyses on the raw MRI data—all processed at a single site—in ENIGMA-OCD we conducted both the two-stage aggregated data meta-analyses and the one-stage IPD-based mega-analyses.

Within ENIGMA-OCD, the meta- and mega-analyses revealed comparable findings for the subcortical regions (Boedhoe et al., 2017), but the mega-analytic approach appeared more sensitive for detecting subtle cortical abnormalities (Boedhoe et al., 2018). We recently empirically evaluated whether a meta-analysis provides results comparable to a mega-analysis, and which of the two analytic frameworks (multiple linear regression mega-analysis model versus linear mixed-effects random-intercept mega-analysis model) performs better. Effect sizes and standard error estimates (and 95% confidence intervals), and (where possible) model fit, assessed using the Bayesian information criterion, were used to evaluate which of the methods performs best. Although effect sizes were similar for the meta-analysis and linear regression mega-analysis, we showed that in the case of

FIGURE 1 World map showing the 34 institutes participating in the ENIGMA-OCD consortium

cross-sectional structural MRI data a mega-analysis performs better than a meta-analysis (lower standard errors and narrower confidence intervals), and in a multi-center study with moderate variation between cohorts, a linear mixed-effects random-intercept mega-analytical framework seems to lead to the best model fit (Boedhoe et al., 2019).

1.3 | First findings of ENIGMA-OCD: Cortical thickness, surface area and subcortical volume

When comparing OCD patients to healthy controls, we analyzed data from adult subjects (18 years and older) and pediatric/adolescent subjects (below 18 years), separately. For the purpose of basic comparisons of subcortical volume and cortical thickness and surface area, we pooled data from children (<12 years) and adolescents (12–17 years) in a pediatric/adolescent analysis (Boedhoe et al., 2017, 2018), but in the subsequent cross-disorder comparisons with other child-onset disorders (autism spectrum disorder, ASD) and attention deficit hyperactivity disorder (ADHD), we analyzed children and adolescents separately (Boedhoe et al., 2019).

In the subcortical analyses, we found clear differences between the pediatric OCD patients (compared with healthy controls, n = 335 and 287, respectively) and the adult OCD patients (compared with healthy controls, n = 1,495 and 1,472, respectively) (Boedhoe et al., 2017). Pediatric OCD was associated with greater volume of the thalamus (Cohen's d = 0.38), but this effect was only detectable in the comparison of unmedicated OCD versus healthy controls. We recently replicated this finding with data from the Generation R cohort (Jaddoe et al., 2010), in which children with probable OCD (scoring above the cut-off on the short OCD screener) also had a larger thalamus, on average (unpublished data). This may suggest altered neurodevelopment in children prone to develop OCD. Nevertheless, the thalamus is not a uniform structure but rather consists of multiple subnuclei, each with its own cortical connectivity profile and functions (Behrens et al., 2003). OCD-related enlargement of the overall thalamus may therefore be driven by one or a few subnuclei. Which subnuclei drive this effect is currently unknown, although shape analysis has revealed increased surface area in anterior and pulvinar nuclei in adult OCD patients (Shaw et al., 2015). In future studies, we will employ the recently developed and validated algorithm from Iglesias et al. (2018) to segment the subnuclei of the thalamus and study which nuclei drive the effect.

Adult OCD patients showed smaller hippocampus (Cohen's d = −0.13), most pronounced in patients with an adult onset of OCD (Cohen's d = −0.18), patients with a comorbid lifetime diagnosis of depression (Cohen's d = −0.27), and patients using medication (Cohen's d = −0.29). Adult OCD patients also showed larger pallidum (Cohen's d = 0.16), most pronounced in patients with a childhood onset of OCD (Cohen's d = 0.25), and patients using medication (Cohen's d = 0.29). The hippocampal findings do not seem to be specific to OCD, as similar results have been reported by the ENIGMA working groups for schizophrenia (Van Erp et al., 2016), bipolar disorder (Hibar et al., 2016), major depressive disorder (Schmaal et al., 2016), and posttraumatic stress disorder (Logue et al., 2018), and so may be related to trans-diagnostic aspects of chronic distress. The pallidum findings fit well with all prior meta- and mega-analyses (De Wit et al., 2014; Peng et al., 2012; Radua et al., 2010; Radua & Mataix-Cols, 2009; Rotge et al., 2010) and appear to be more specific to OCD. Larger pallidum could be due to chronic compulsivity (Van den Heuvel et al., 2016). At the same time, since larger pallidum has also been reported in schizophrenia (Van Erp et al., 2016), use of antipsychotic medication might partly explain the findings. Indeed, in our analysis by age-group and medication class (Ivanov et al., 2019), a

larger pallidum was seen particularly in adolescent and adult patients taking antipsychotics.

Analyses of alterations in brain asymmetry, in partnership with ENIGMA's Laterality working group, showed that children/adolescents with OCD (n = 501) versus healthy controls (n = 439) have altered asymmetry of the thalamus (more leftward; Cohen's d = 0.19) and pallidum (less leftward, Cohen's d = –0.21), which was not detectable in adult OCD, possibly reflecting altered neurodevelopmental processes (Kong et al., 2019; Figure 2).

The cortical analyses showed that pediatric/adolescent OCD patients (n = 407) versus healthy control children/adolescents (n = 324) have thinner left and right inferior parietal, left superior parietal and lateral occipital cortices (Cohen's d values between –0.24 and – 0.31). Adult OCD patients (n = = 1,498), in comparison to adult healthy controls (n = 1,436), showed a lower surface area of the transverse temporal cortex (Cohen's d = –0.16) and a thinner bilateral inferior parietal cortex (Cohen's d = –0.14; Boedhoe et al., 2018). The involvement of the parietal cortex is consistent with the vertex-wise FreeSurfer findings of the OBIC consortium (Fouche et al., 2017), and the effect was now further found to extend to children, suggesting altered maturation of the parietal cortex early in life that persists into adulthood. One obvious discrepancy with previous meta- and mega-analysis of structural MRI in OCD is the lack of involvement of the prefrontal regions; this may reflect differences in methods used: The atlas-based approach to cortical thickness and surface areas that has been used in ENIGMA (segmenting whole structures using coarse parcellation) can be less sensitive to subtle regional abnormalities than VBM's voxel-wise registration and vertex-based approach to cortical thickness that was used by OBIC. The use of higher-resolution parcellation methods (e.g., Glasser et al., 2016) might give results that are more consistent with the voxel-wise and vertex-wise approaches.

Medication status appeared to be a strong confounder (Boedhoe et al., 2018). Compared to healthy controls (n = 324), pediatric/adolescent OCD patients on medication (n = 183) had thinner inferior and superior parietal and lateral occipital cortices (Cohen's d = –0.31) and widespread surface area differences, mainly in frontal regions (Cohen's d values between –0.27 and –0.33). Medicated adult OCD patients (n = 646), in comparison to controls (n = 1,436), had widespread abnormalities in cortical thickness, mainly in relation to frontal, temporal, parietal and occipital regions (Cohen's d values between –0.10 and –0.26, see Figure 3). Unmedicated pediatric/adolescent (n = 222) and adult (n = 831) OCD patients did not differ from healthy controls, on average, in cortical thickness and surface area. Medication effects were most pronounced in those patients using a combination of antidepressants and antipsychotics, and persisted after adjusting for disease severity and co-morbidity. Although these medication effects should be interpreted with caution due to the cross-sectional nature of the study design and lack of information on duration and dosage of medication use, they may suggest neuroplastic effects of medication on the brain, both in children and adults. Longitudinal studies of the long-term protective and potentially negative effects of antidepressants on the developing brain are non-existent. This knowledge gap is remarkable in the context of more than 60 years of antidepressant prescriptions. Solid conclusions on the impact of this medication on the brain await longitudinal studies, with detailed assessment of symptom profile, duration without treatment, medication dosage and duration of exposure, also taking into account the exposure to other interventions (e.g., CBT) and environmental factors (e.g., early life stress).

Using the available cross-sectional data of ENIGMA-OCD, we studied medication effects in two additional ways. First, we used machine learning analysis of the previously analyzed cortical and subcortical measures from 2,304 OCD patients and 2,068 controls to assess whether anatomical group differences might be used to create a neuroimaging biomarker for OCD (Bruin et al., 2019). Classification performance across 10 different machine and deep learning approaches was limited, in this initial analysis that only used extracted measures derived from anatomical MRI. With site-stratified cross-validation, the receiver operating characteristic area under the curve (ROC-AUC) ranged between 0.57 and 0.62, and the performance dropped to chance level (classification performance between 0.51 and 0.54) when leave-one-site-out cross-validation was used, indicating that these anatomical brain features, on their own, are not suitable as a biomarker for OCD. However, when patients were stratified according to whether they currently use medication, classification performance improved remarkably: Medicated OCD patients and healthy controls could then be distinguished with a 0.73 AUC (SD = 0.03, p_{corr} < .001) (in contrast to unmedicated OCD and healthy controls, with 0.61 AUC [SD = 0.02, p_{corr} = .03]), and medicated and unmedicated OCD patients with 0.86 AUC (SD = 0.02, p_{corr} < .001).

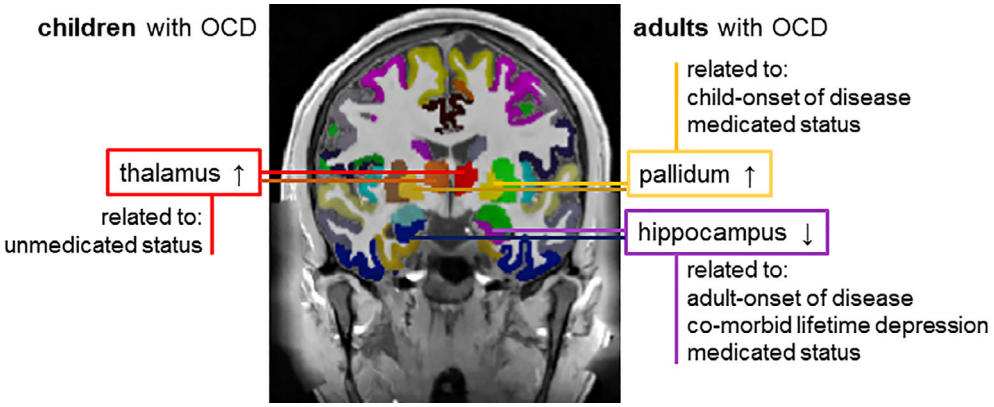

FIGURE 2 Summary of the subcortical volume effects in ENIGMA-OCD (based on Boedhoe et al., 2017 Am J Psychiatry)

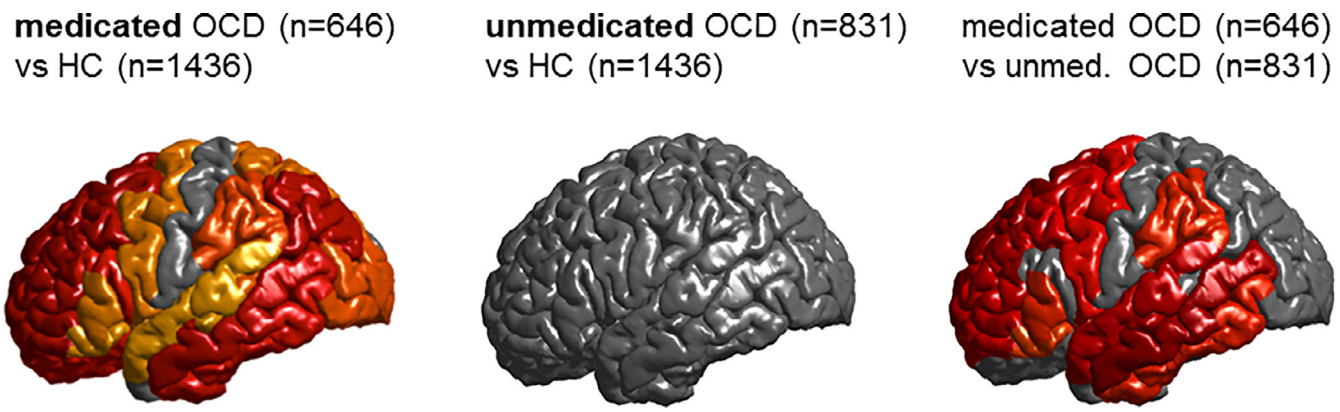

FIGURE 3 Summary of the cortical thickness effects in adult OCD patients compared to healthy controls in ENIGMA-OCD, in relation to medication status (based on Boedhoe et al., 2018 Am J Psychiatry). Negative effect sizes *d* (ranging from light orange *d* = −0.05 to dark red *d* = −0.15) indicate thinner cortex in OCD compared to controls

These multivariate results therefore mirror the univariate results, and highlight that medication use is associated with significant differences in brain anatomy.

In the second additional approach, we studied age-by-medication interactions in 2,176 OCD patients (1,040 medicated/1,136 unmedicated) and 2,003 healthy controls, using a general linear model (Ivanov et al., 2019). Medicated OCD patients, unmedicated OCD patients, and healthy controls all showed decreasing brain-wide cortical thickness, surface area, and subcortical volume with increasing age ($p < .0005$) in most regions. Effects of medication ($p < .001–.0005$) and age-by-medication interactions ($p < .05–.0005$) were detected in 46 cortical and 7 subcortical brain regions. Accordingly, in certain regions (e.g., supramarginal gyrus, lateral occipital cortex), child and/or adolescent medicated OCD patients had thicker cortex than unmedicated patients. Adult medicated OCD patients, however, had thinner cortex than unmedicated OCD patients. Effects on cortical thickness were strongest for tricyclic antidepressants, but were also present for serotonin reuptake inhibitors (SRIs) and benzodiazepines. One (speculative) explanation of the differential effects of medication on cortical thickness in pediatric versus adult patients with OCD is the combination of treatment-associated slowing of the neuronal regressive changes (synapse loss and neurite pruning) and slowing (in children) and acceleration (in adults) of the progressive white-matter myelination of normal aging.

1.4 | The first ENIGMA-OCD brain structural connectivity results

After conducting the initial meta- and mega-analyses of regional brain volumetric abnormalities, we initiated analyses of structural brain connectivity, using both structural covariance graph analyses (Yun et al., 2020) and diffusion tensor imaging (Piras et al., 2019). Brain structural covariance networks reflect covariation in morphology of different brain areas and are thought to reflect common trajectories in brain development and maturation, as well as common effects of a disorder (Hunt et al., 2016). Large-scale investigation of structural covariance networks are therefore of specific interest when studying neurodevelopmental disorders such as OCD that have chronic symptoms over the lifespan.

Using T1-weighted MRI derived measures of brain morphometry (bilaterally-averaged values of 33 cortical surface areas, 33 cortical thickness values, and six subcortical volumes) from OCD patients ($n = 1,616$) and healthy controls ($n = 1,463$), we calculated intra-individual brain structural covariance networks, in which edge weights were proportional to the similarity between two brain morphological features in terms of deviation from controls (*z*-score transformed; Yun et al., 2020). We focused on measures of network segregation (clustering and modularity), network integration (global efficiency), their balance (small-worldness), and community membership. We also studied hub profiling of regional brain areas using measures of betweenness, closeness, and eigenvector centrality. Individually calculated network measures were integrated across the 37 ENIGMA-OCD datasets using a meta-analytic approach. At the global level, compared to healthy controls, OCD patients showed lower clustering ($p < .0001$), modularity ($p < .0001$), small-worldness ($p = .017$), and community membership, suggesting lower network segregation. At the regional level, compared to healthy controls, OCD patients showed lower (rank-transformed) centrality values for caudate and thalamus volume, and surface area of paracentral cortex, suggesting an altered distribution of brain hubs. Centrality, mainly of the cingulate and orbitofrontal areas, was associated with OCD disease duration, indicative of greater involvement of these regions with chronicity.

Abnormalities in structural connectivity might be explained in part by microstructural alterations in white matter. A number of the ENIGMA-OCD sites ($n = 19$) also have diffusion tensor imaging (DTI) scans of the same participants used in the analyses of the T1-weighted MRI measures. We compared DTI-derived values for fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) in 25 brain regions of OCD patients ($n = 700$ adults and 174 children/adolescents) and healthy controls

(n = 645 adults and 144 children/adolescents) (Piras et al., 2019). We meta-analyzed patient versus control differences across sites, adjusted for age and sex, and investigated potential associations with clinical characteristics, such as medication status, age of disease onset, duration of illness, and disease severity. Adult OCD patients showed significantly lower FA in the sagittal stratum (Cohen's d = −0.21) and posterior thalamic radiation (Cohen's d = −0.26). Lower FA in the sagittal stratum was associated with a younger age of onset (z = 2.71), longer duration of illness (z = −2.09), and a higher percentage of medicated patients in the cohorts studied (z = −1.98). No significant association with symptom severity was detected. Pediatric OCD patients did not show any detectable microstructural abnormalities compared to matched healthy controls. These results suggest that in adult OCD patients the reported microstructural alterations in projection and association fibers to posterior brain regions are partly related to disease course and medication status, and thus are likely more a consequence than a cause of disease.

Since brain morphometry is plastic and changes under the influence of daily behavior and network function, the next level of understanding is to link these morphometric features of disease to alterations in brain network function, using fMRI scans, both at rest and during specific cognitive or emotional states.

1.5 | New perspectives with clinical relevance

The ENIGMA-OCD consortium has already demonstrated significant scientific relevance by increasing our understanding of the disorder. Large-scale worldwide collaboration has also been relevant to thinking through more effective and efficient ways of doing science by bringing together data, expertise, and a critical mass of investigators. Regarding clinical significance, the machine learning analyses of morphological measures of the brain are not yet valuable diagnostically (Bruin et al., 2019), and we certainly do not need an MRI scan to diagnose OCD. However, performance is likely to improve with the inclusion of multimodal features from diffusion-weighted and functional MRI. However, several important lessons with clinical relevance have emerged. One example is the unexpected, but robust finding that medication status and disease chronicity both have a marked impact on all brain measures analyzed to date. This has two direct implications: First, it emphasizes the importance of establishing longitudinal studies to examine the beneficial and potential harmful effects of medication on the developing brain and; second, the fact that disease chronicity is related to marked morphological alterations of the brain might provide additional incentive to invest in the implementation of state-of-the-art interventions (e.g., exposure treatment requires significant scale up across the globe) and the development of innovative treatments for those who do not respond to first line interventions.

Another example of clinical relevance of ENIGMA-OCD is the potential for discovering prognostic biomarkers, that is, the prediction of treatment response based on morphometric and/or functional brain signatures. For instance, response to cognitive behavior therapy (CBT) has been linked to structural variability in the prefrontal cortex (Fullana et al., 2014; Hoexter et al., 2013) and activation and connectivity of the amygdala (Fullana et al., 2017; Göttlich, Krämer, Kordon, Hohagen, & Zurowski, 2015; Olatunji et al., 2014). Prediction studies have been so far limited in sample size and therefore replicability of findings has been poor. We have now started using data from ENIGMA-OCD samples with longitudinal clinical data of 170 children with OCD (from nine sites) and 315 adults with OCD (from seven sites), to study how variation in morphological values (cortical thickness, surface area, and subcortical volumetry) is related to variation in treatment response (Bertolin, Martinez-Zalacain, Boedhoe, & Alonso, 2019). Moreover, we expect that multimodal imaging approaches, combining data on morphological features with measurements of white matter integrity and information on network function using resting-state fMRI, will be more informative for predicting treatment response at the individual level using machine learning analyses.

1.6 | Ongoing and future analyses within ENIGMA-OCD

As already shown in previous meta-analyses across related mental disorders, some neural correlates are common across mental disorders, whereas others are more disorder-specific (Goodkind et al., 2015; Radua et al., 2010). The ENIGMA consortium, with different working groups using the same pipelines for data processing and data analysis, is an ideal setting for studying common and distinct features of mental disorders. Our first attempt to do so focused on neurodevelopmental disorders in the impulsive-compulsive spectrum, comparing OCD with ASD and ADHD. Using structural T1-weighted MRI scans from 151 cohorts worldwide with data from patients with OCD (n = 2,323), ASD (n = 1,777), and ADHD (n = 2,271), and matched healthy controls (n = 5,827), we performed a mega-analysis of cortical thickness, surface area and subcortical volume across groups, with separate analyses for children (<12 years), adolescents (12–17 years), and adults (>18 years) (Boedhoe et al., 2019). We found no shared alterations among all three disorders (even with uncorrected analyses), while shared alterations between any two disorders did not survive correction for multiple comparisons. Children with ADHD compared to those with OCD had smaller hippocampal volumes. Children and adolescents with ADHD also had smaller intracranial volume than control children and those with OCD or ASD. Adults with ASD showed thicker frontal cortices compared to adult controls and other clinical groups. OCD-specific alterations were not found across different age-groups and no surface area alterations were found across the disorders. Based on the literature, future cross-disorder comparisons between OCD and other anxiety disorders, as previously done by Radua et al. (2010), as well as comparison with schizophrenia, which is also characterized by a bigger pallidum (Van Erp et al., 2016) may be useful.

Another direction of research that is currently in preparation is the meta-analysis of resting-state functional MRI. Resting-state fMRI

(rs-fMRI) can provide multiple measures of functional connectivity that are thought to index the communication between distinct brain regions. A recent meta-analysis based on reported findings in the literature found that multiple resting-state networks are affected in OCD (Gursel et al., 2018). Moreover, a single-site study suggests that rs-fMRI can predict the outcome of CBT (Reggente et al., 2018). To obtain robust estimations of functional connectivity abnormalities in OCD, the consortium aims to perform functional connectivity analyses using the *fmriprep* + pipeline that has been developed by Veer and colleagues (Charité, Berlin). This pipeline uses the fMRI preprocessing stages from *fmriprep* (Esteban et al., 2019), and outputs various rs-fMRI measures such as resting-state networks based on independent components analysis and (partial) correlation matrices between distinct brain regions. Initially, the consortium will analyze average group differences in these measures between OCD patients and controls, and subsequently use machine-learning methods to determine whether rs-fMRI can provide a biomarker for OCD. Furthermore, the same methods will be used in order predict CBT outcome at the group and individual patient level. We hope that this endeavor will provide a biomarker for treatment outcome that generalizes to different sites, and thereby paves the way towards personalized treatment for OCD. In the future, we hope to extend rs-fMRI meta-analysis in ENIGMA-OCD to task-based fMRI, focusing on frequently used paradigms such as emotional processing, response inhibition (and other executive tasks), and decision-making.

Advances in large-scale neuroimaging studies have allowed the characterization of distinct group differences in the macroscopic structure of the cerebral cortex, across several psychiatric disorders (Thompson et al., 2019). Using a new bioinformatics approach, named virtual histology, we can now link these macroscopic differences with microscopic histological features within the human cerebral cortex (Patel, Shin, Gowland, Pausova, & Paus, 2018; Shin et al., 2018). In brief, virtual histology relates variation in cell-specific gene expression profiles across the 34 regions of the Desikan-Killiany atlas with profiles of group differences in cortical thickness across the same 34 regions (Desikan et al., 2006). This approach combines gene expression data from the Allen Human Brain Atlas (Hawrylycz et al., 2012), and cell-specific markers from single-cell RNA sequencing (Zeisel et al., 2015) with MRI derived measures. Profiles of group differences in cortical thickness are generated using a meta-analytic approach for each of six major psychiatric disorders (ASD, ADHD, bipolar disorder, major depressive disorder, OCD, and schizophrenia). Currently, there are 12,006 cases and 14,842 controls contributing to these profiles. The goal of the project is to characterize cell types within the human cortex (neurons [pyramidal cells and interneurons] and glia [astrocytes, microglia, oligodendrocytes]) in which gene expression is correlated with differences in cortical thickness across disorders, in the hope of illustrating common and/or unique neurobiological correlates between these disorders.

Ultimately we would like to combine imaging data with genetic information. ENIGMA has developed pipelines for integrated analyses of both neuroimaging and genetic data. Some of this work has focused on common variants: Satizabal et al. (2019), for example, investigated nearly 40,000 individuals, and found that more than 45 genetic loci were significantly associated with subcortical volumes. Analyses indicated that associated genes are implicated in neurodevelopment, synaptic signaling, axonal transport, and other key processes. Other work has focused on CNVs: in the largest CNV neuroimaging study to date, for example, 15q11.2 BP1-BP2 structural variation was found associated with brain morphology and cognition, with deletion carriers being particularly affected (Writing Committee for the ENIGMA-CNV Working Group., 2019). There is a clear potential to extend such work to specific disorders such as OCD. In a proof of principle investigation, ENIGMA-OCD has explored the overlap in genetic contributions to subcortical volumes and OCD (Hibar et al., 2018); significant positive concordance was found between OCD risk variants and variants associated with greater nucleus accumbens and putamen volumes. Further work is needed to expand on these preliminary findings. While the combined imaging-genetics database is still small, a polygenic risk score approach may be a useful first step.

1.7 | Limitations of the ENIGMA approach

Three important methodological weaknesses of the ENIGMA-OCD concept should be mentioned. First, the data collection was done in the past, at a time when there was no plan to use the data in worldwide collaboration. Therefore, there has been no harmonization of data acquisition, either with respect to imaging data or with respect to inclusion criteria and clinical data. Various MRI machines (with different field strengths) and various scan sequences have been used with inevitable variations in data quality. In addition, the level of detail on the clinical phenotypes (disease severity, comorbidity, disease course, treatment history, etc.) is limited, so disallowing detailed analyses of symptom profiles or cross-disorder characteristics. Second, the data collection has been mostly cross-sectional, limiting our ability to answer questions related to disease course, effects of medication, and cause versus consequence of disease. Longitudinal data is highly warranted, and with the increase in pre-/post-treatment imaging studies, we expect that more longitudinal data will soon become available. Family and particularly twin studies could go a long way to disentangle vulnerability from disease chronicity and medication. Third, only some of the imaging samples also have genotyping data, presenting a challenge, since for imaging-genetic analyses large samples are needed.

1.8 | Summary and future directions in global collaborations

ENIGMA-OCD has brought together OCD experts from all over the world to re-analyze historical MRI data using meta- and mega-analyses. This has not only resulted in important contributions to the literature on brain alterations in OCD, but has also stimulated international collaboration and sharing of OCD imaging data from sites across the globe. While as outlined earlier, there are many

questions still to address in the growing ENIGMA-OCD dataset, the findings and the successful model of international collaboration have already spurred new studies. For example, to address the lack of harmonization of data acquisition and the lack of detail on clinical profile, and to address the confound of medication in the ENIGMA-OCD dataset, five of the participating ENIGMA-OCD sites, representing five continents, are now funded by NIMH (PI: H. Blair Simpson) to conduct the largest neurocognitive and multimodal-imaging study in medication-free subjects with OCD to date. Specifically, we will recruit 250 medication-free adults with OCD, 100 unaffected adult siblings of individuals with OCD, and 250 healthy control subjects. All will receive clinical evaluation, neurocognitive assessment, and MRI, focusing on morphometry (T1-weighted MRI), structural connectivity (DTI), and functional connectivity (rs fMRI). To ensure harmonized data collection, we have developed detailed protocols to ensure cross-site reliability on clinical measures, standardized delivery of neurocognitive tasks, and optimal MRI data acquisition for data pooling (see Simpson et al., 2020 for details). Following best-practices used in large-scale imaging consortia, the MRI quality procedures include: Harmonization of scan sequences to optimize scan quality across scanners; both human and physical phantom studies at study start, with repeat phantom studies and preprocessing of all scans in real-time to ensure maintenance of scan quality over the course of study recruitment. Other ENIGMA-OCD sites that start new data collection might consider using similar methods, to increase the number of samples with higher quality harmonized data.

To conclude, large-scale data-sharing as facilitated by ENIGMA-OCD has accelerated discovery and generated novel hypotheses that are now being pursued. It has also created a model for large-scale global collaboration across OCD experts, and even more broadly, across working groups focused on a range of disorders and methodologies. By joining forces, we can help to shift the research model from local and mono-disciplinary to global and multidisciplinary, increase rigor and transparency, and accelerate discovery. In the end, we share a common goal: To develop a circuit-based approach to different cognitive and clinical dimensions of OCD that can help transform how OCD and related mental disorders are conceptualized, diagnosed, and ultimately treated around the world.

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DATA AVAILABILITY STATEMENT

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