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REVIEW ARTICLE

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Consortium neuroscience of attention deficit/hyperactivity disorder and autism spectrum disorder: The ENIGMA adventure

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Abstract

Neuroimaging has been extensively used to study brain structure and function in individuals with attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) over the past decades. Two of the main shortcomings of the

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neuroimaging literature of these disorders are the small sample sizes employed and the heterogeneity of methods used. In 2013 and 2014, the ENIGMA-ADHD and ENIGMA-ASD working groups were respectively, founded with a common goal to address these limitations. Here, we provide a narrative review of the thus far completed and still ongoing projects of these working groups. Due to an implicitly hierarchical psychiatric diagnostic classification system, the fields of ADHD and ASD have developed largely in isolation, despite the considerable overlap in the occurrence of the disorders. The collaboration between the ENIGMA-ADHD and -ASD working groups seeks to bring the neuroimaging efforts of the two disorders closer together. The outcomes of case–control studies of subcortical and cortical structures showed that subcortical volumes are similarly affected in ASD and ADHD, albeit with small effect sizes. Cortical analyses identified unique differences in each disorder, but also considerable overlap between the two, specifically in cortical thickness. Ongoing work is examining alternative research questions, such as brain laterality, prediction of case–control status, and anatomical heterogeneity. In brief, great strides have been made toward fulfilling the aims of the ENIGMA collaborations, while new ideas and follow-up analyses continue that include more imaging modalities (diffusion MRI and resting-state functional MRI), collaborations with other large databases, and samples with dual diagnoses.

KEYWORDS
ADHD, ASD, cortex, ENIGMA, neuroimaging, subcortical volumes

1 | INTRODUCTION

Two of the most frequently diagnosed neurodevelopmental disorders are attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), which occur in 5–7% and 1–2.8% of children, respectively (Baird et al., 2006; Faraone et al., 2015; Thomas, Sanders, Doust, Beller, & Glasziou, 2015; Xu et al., 2018). Both disorders may persist across the lifespan (Nylander, Holmqvist, Gustafson, & Gillberg, 2013). ADHD is characterized by age-inappropriate, impairing and persisting levels of inattention and/or hyperactivity/impulsivity (American Psychiatric Association, 2013), while ASD is characterized by impaired communication, social interaction skills, and repetitive and restricted behavior (American Psychiatric Association, 2013). Up until 2013, when the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) was published, the presence of an ASD diagnosis excluded a diagnosis of ADHD. Hence, dual diagnosis of both disorders did not officially exist. The research fields for both disorders therefore developed largely in isolation. However, the current diagnostic guidelines of the DSM-5 allow for their dual diagnosis, which has led to the rise of a new field of research studying the overlap between ADHD and ASD. Research in recent years has shown that ADHD is the most common comorbidity in children with ASD (Joshi et al., 2017); 40–70% of children with ASD have comorbid ADHD (Joshi et al., 2017; Kaat, Gadow, & Lecavalier, 2013; Salazar et al., 2015). Of children with ADHD, 15–25% show clinically relevant ASD symptoms (Cooper, Martin, Langley, Hamshere, & Thapar, 2014; Kotte et al., 2013), and 12% meet criteria for an ASD diagnosis (Jensen & Steinhausen, 2015). A large-scale twin study also demonstrated that patients with ASD have a much higher chance of having ADHD than the general population (OR = 22.33) (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). Another twin study indicated that children diagnosed with one of the two disorders often show features of the other, even in the absence of a full comorbid diagnosis (Ghirardi et al., 2018).

In addition to the frequent co-occurrence of both disorders in the population, ADHD and ASD partly overlap in their pathophysiology and phenomenology in socialization and communication domains (e.g., [Antshel, Zhang-James, & Faraone, 2013]). Latent class analyses of both clinical and community-based samples dissociated four distinct patient groups—ADHD, ADHD + ASD, ASD + ADHD, and ASD—with the middle two patient groups showing symptoms of both disorders, with either one dominating the clinical picture (van der Meer et al., 2012). These findings gave rise to the hypothesis that ADHD and ASD may be viewed as different manifestations of the same overarching disorder, with each diagnosis representing the extreme end of a complex multivariate trait and with most clinical cases presenting various combinations of ADHD and ASD symptoms (Antshel, Zhang-James, Wagner, Ledesma, & Faraone, 2016). Even without hypothesizing about a single, overarching disorder, it is well accepted that core features of both ADHD and ASD—in particular inattention and social

deficits—overlap, and that partly, but not fully, overlapping patterns are found in cognitive and behavioral traits associated with ADHD and ASD traits (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011; Truedsson, Bohlin, & Wåhlstedt, 2015; van der Meer et al., 2017). Such hypothesis would lead to the abandonment of viewing ADHD and ASD as opposing phenotypes (e.g., Mayes, Calhoun, Mayes, & Molitoris, 2012).

Given the common background between these two disorders, the work done in the ENIGMA ADHD and ASD working groups may be used to further our understanding of both the unique and common neurobiological aspects of both disorders.

1.1 | The genetic background of ADHD and ASD

Further evidence for commonalities between ADHD and ASD comes from genetic research. Genetically, ADHD and ASD are both complex disorders, influenced by environmental and genetic susceptibility factors. Results from family, twin and adoption studies converge to suggest that both ADHD and ASD have a high heritability (75 and 90%, respectively; Faraone & Larsson, 2019; Freitag, 2007). Both common and rare genetic variants contribute to this heritability (Satterstrom et al., 2019), and part of this heritability is shared by the two disorders (Faraone & Larsson, 2019; Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010; Ronald & Hoekstra, 2011). Considering common genetic variants, large-scale genome-wide association studies (GWAS) meta-analyses confirmed that ADHD and ASD are significantly genetically correlated (37%; Lee et al., 2019). Similarly, in the general population, the genetic backgrounds of ADHD and ASD were also found to be partly shared throughout childhood and adolescence (Stergiakouli et al., 2017). Rare variants with strong effect sizes directly explain ASD or ADHD in a relatively small number of people only, though many such variants are known to contribute to each disorder or both (e.g., Satterstrom et al., 2019). Many of the genes hit by such rare risk variants are also likely to converge on biological processes (Bourgeron, 2015) that are shared by ASD and ADHD (and other neurodevelopmental disorders; Cristino et al., 2014; Schork et al., 2019). These processes include those involved in chromatin remodeling and transcription, protein synthesis and degradation, synaptic receptors and cell adhesion molecules, and scaffolding proteins (Luo, Zhang, Jiang, & Brouwer, 2018).

1.2 | Neuroimaging across the lifespan in ADHD and ASD before the founding of ENIGMA-ADHD and ENIGMA-ASD

In the past decades, many neuroimaging studies have investigated the structure and function of the brains of individuals with ADHD and ASD. Within the ADHD literature, most studies showed structural case–control differences across a wide variety of brain regions, in children but also in adults with ADHD (Faraone et al., 2015; Franke et al., 2018). Further, ADHD symptom ratings in the population were found to be negatively associated with, for example, thickness of the cortex (Mous et al., 2014; Shaw et al., 2011). A total of five meta-analyses based on case–control studies have tried to identify common differences in brain structure associated with ADHD, based on case–control studies (Ellison-Wright, Ellison-Wright, & Bullmore, 2008; Frodl & Skokauskas, 2012; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Norman et al., 2016; Valera, Faraone, Murray, & Seidman, 2007). The most consistent results across those meta-analyses were reduced volumes of (parts of) the striatum in patients compared to controls. Two of those five studies reported that striatal structural differences between individuals with ADHD and controls decreased with increasing age, and that stimulant treatment was associated with normalizing effects on the brain volume differences (Frodl & Skokauskas, 2012; Nakao et al., 2011). This work highlighted the role of the striatum in the ADHD pathology. Limitations of these meta-analyses included the limited ability to investigate the role of individual variables on the identified brain differences, such as comorbidities, medication use, but also age, and the inability to look at lifespan trajectories. Such lifespan trajectories are of interest in ADHD because longitudinal studies of brain volume suggest a delay of brain maturation for individuals with ADHD, but of yet unknown significance for remittance and persistence of ADHD into adulthood (Shaw et al., 2007, 2011).

Much of the research done on ASD has focused on the role of subcortical brain abnormalities (Amaral, Schumann, & Nordahl, 2008). Both larger (Turner, Greenspan, & van Erp, 2016) and smaller (Sussman et al., 2015) volumes of striatal structures have been reported, while higher average intracranial volume, total gray matter, and cortical thickness have also previously been found in ASD (Fombonne, Rogé, Claverie, Courty, & Frémolle, 1999; Haar, Berman, Behrmann, & Dinstein, 2016), with more specific cortical effects in the frontal and temporal lobes (Foster et al., 2015; Zielinski et al., 2014). Altered frontal and striatal volumes and disrupted fronto-striatal connectivity are key components in the executive function deficit theory of ASD (Di Martino et al., 2011; Langen et al., 2012). On the other hand, abnormal amygdala volumes, specifically in childhood, may be related to the social theories of ASD (Baron-Cohen et al., 2000). However, the neuroimaging literature is not consistent as far as the direction and effect size of these morphometric brain differences go (Nickl-Jockschat et al., 2012; Stanfield et al., 2008). The introduction of the ABIDE consortium—a publicly available data set of MRI data from 13 existing cohorts—has not managed to reduce much of the pre-existing heterogeneity, as analyses (Haar et al., 2016) showed only very small local associations of ASD with brain morphometry, perhaps questioning the presence of structural differences in ASD altogether.

Several small scale studies have examined differences and overlap in brain structure between ADHD and ASD, reporting overlapping structural brain alterations in the temporal and parietal areas (Brieber et al., 2007), inferior frontal cortex (Geurts, Ridderinkhof, & Scholte, 2013), cerebellum, corpus callosum (Dougherty, Evans, Myers, Moore, & Michael, 2016), as well as white matter (Ameis et al., 2016). A study of white matter organization in children with ADHD, ASD, and controls observed transdiagnostic associations

between continuous measures of ASD symptoms and inattention (but not total ADHD symptoms) and indexes of white matter organization, particularly in the corpus callosum (Aoki et al., 2017). An analysis of intrinsic connectivity in cases with ADHD, ASD, and controls found evidence for both shared and distinct underlying mechanisms at the large-scale network level. Shared connectivity alterations were found in the precuneus, whereas ADHD-specific increases in degree centrality were assessed in right striatum/pallidum, and ASD-related increases in degree centrality in bilateral temporolimbic areas (Di Martino et al., 2013). Overall, there is a distinct lack of well-powered cross-disorder studies that include both cases with ADHD and ASD (Rommelse, Buitelaar, & Hartman, 2017). Furthermore, the few existing studies focused solely on children, leaving the overlap between ADHD and ASD over the lifespan almost completely unknown.

Taken together, the pre-existing literature on brain imaging in ADHD and ASD still shows considerable gaps as well as opportunities for improvement. Two of the main shortcomings remain to be the small sample sizes and the wide heterogeneity in the methodology used, both of which have likely contributed to the difficulty in replicating imaging findings. Opportunities to remedy at least some of these shortcomings are facilitated by the ENIGMA consortium. Over the past decade, this consortium has provided a platform for combining genetic and brain imaging datasets (Adams et al., 2016; Hibar et al., 2015, 2017; Stein et al., 2012), while using unified preprocessing and analysis pipelines to substantially increase sample sizes and decrease methodological heterogeneity as well as allow direct comparison between different disorders such as ADHD and ASD. Working groups for ADHD and ASD research were founded under ENIGMA's umbrella in 2013 and 2014, respectively, with the following aims: (a) reduce methodological heterogeneity in neuroimaging studies that might cause differences in findings across studies; (b) increase power to identify (new) characteristics of individuals with ADHD and ASD; (c) cross-sectionally map the lifespan trajectory of brain characteristics of ADHD and ASD; and (d) combine expertise and join forces from around the world on brain research for ADHD and ASD to boost our understanding of the brain in ADHD and ASD. Both working groups' initial projects focused on subcortical brain volume and cortical thickness and surface area analyses.

2 | KEY FINDINGS FROM THE ENIGMA-ADHD AND ENIGMA-ASD STUDIES: SUBCORTICAL AND CORTICAL MEASURES

In the ENIGMA-ADHD's first project, the volumes of subcortical structures including nucleus accumbens, amygdala, caudate nucleus, globus pallidus, hippocampus, thalamus, putamen, and also the total intracranial volume (ICV) were compared between cases with ADHD and controls. These regional brain volumes were segmented based on protocols provided by ENIGMA using FreeSurfer software. All participating sites segmented their raw data and quality checked of these segmentations locally using protocols provided by ENIGMA. Detailed instructions for analysis and quality control are found on the ENIGMA website (http://enigma.ini.usc.edu/protocols/imaging-protocols/). The resulting outputs were sent by each site to the coordinator of ENIGMA-ADHD. Analyses were performed on data collected at 23 sites, that included a total of 1,713 cases with ADHD and 1,529 controls, with an age range of 4–63 years of age. A cross-sectional mega-analysis examined case–control differences within the whole sample, and also separately in children (<15 years), adolescents (15–21 years), and adults (>21 years). A linear mixed model was run with age, sex, and ICV as fixed variables and site as a random variable. Results for the total sample showed significant but small differences in the total volume of nucleus accumbens (Cohen's $d = -0.15$), amygdala ($d = -0.19$), caudate nucleus ($d = -0.11$), hippocampus ($d = -0.11$), putamen ($d = -0.14$), and ICV ($d = -0.10$), where the subjects with ADHD had smaller volumes as compared to controls (Hoogman et al., 2017). A follow-up meta-analysis confirmed the mega-analysis results. When age groups were considered, case–control differences were only significant in children. No effects of psychostimulant use or of present comorbidities were found, nor were there any detectable effects of ADHD severity (symptom counts). However, the statistical power for these latter analyses was lower as the availability of these variables in the varied at 25–50% of the total sample.

The second main analysis of the working group covered the cortex, where cortical thickness and surface area were calculated on 34 region segmentations from the Desikan-Killiany atlas (Desikan et al., 2006; Hoogman et al., 2019). Since completion of its subcortical project, ENIGMA-ADHD had grown to 36 sites including 4,180 individuals—2,246 with ADHD and 1,934 control subjects which were included in the cortical project. Results showed, on average, lower surface area in frontal, cingulate, and temporal regions in the analysis of children with ADHD versus controls, with the largest case–control effect sizes in the youngest group of children. The largest effect was found for total surface area ($d = -0.21$). Lower cortical thickness values were found for the fusiform gyrus and temporal pole in children with ADHD compared to controls. Neither surface area nor thickness differences were found in the adolescent and adult groups. In collaboration with the Generation-R study (White et al., 2018), a pediatric population study in Rotterdam, The Netherlands, ENIGMA-ADHD found that symptoms of inattention were negatively associated with total surface area, and the surface area of two regions that had shown significant case–control differences in the initial ENIGMA-ADHD analyses. In other words, case–control effects in the caudal middle frontal gyrus and middle temporal gyrus were also detected in a nonclinical population sample of children 10 years of age. Similar trends were seen for other regions, such as in one of the ENIGMA-ADHD samples ($n = 506$), called NeuroIMAGE (von Rhein et al., 2015), significant regions from the ENIGMA-ADHD analysis were compared between cases, their unaffected siblings and unrelated typically developing controls to investigate familial effects. Compared to controls, the unaffected siblings had lower on average surface area values for caudal middle frontal gyrus, lateral orbital frontal gyrus, superior frontal gyrus, and total surface area. However, mean values did not differ

significantly from their affected siblings (Hoogman et al., 2019). Since siblings share 50% of their genes, these data suggest that familial factors, genes and/or shared environment, may play a role in the cortical differences observed in ADHD.

In the ENIGMA-ASD working group, findings from the subcortical volume and cortical thickness/surface area analyses were published in a joint manuscript (van Rooij et al., 2018). The preprocessing and analysis pipelines followed were identical to those used in the ADHD working group analyses. A total of 52 sites were included in this primary analysis, with a total of 1,571 cases with ASD and 1,651 controls. The cross-sectional ASD mega-analysis was performed over the entire age range. Small but significant deficits were found in the subcortical volumes of the pallidum (d = −0.08), putamen (d = −0.10), amygdala (d = −0.08), and nucleus accumbens (d = −0.13). Cortical analysis showed no detectable differences in regional and total surface areas. However, cases with ASD showed greater cortical thickness in frontal brain areas, and lower cortical thickness in temporal/occipital brain areas (d = −0.21 to d = 0.2). The effects of age were uniform over all subcortical and cortical findings as all showed a distinct peak difference between cases with ASD and controls around adolescence, but a normalization in adults.

3 | OVERLAP AND DIFFERENCES BETWEEN THE CASE–CONTROL STUDIES OF ADHD AND ASD FOR SUBCORTICAL AND CORTICAL MEASURES

When examining the main results from the cortical and subcortical analyses of the ENIGMA-ADHD and ASD working groups, we can readily observe several common and distinct patterns (Hoogman et al., 2017; Hoogman et al., 2019; van Rooij et al., 2018). The two cohorts were strikingly similar in the subcortical volume analysis, as both disorders show comparable decreases in putamen, amygdala and nucleus accumbens volumes when compared to controls (see Figure 1 and Table 1). Cortical thickness measures also showed some comparable effects between the ADHD and ASD publications as both disorders were associated with lower thickness in the temporal lobes, yet only ASD showed increased cortical thickness, specifically in the frontal lobe (see Figure 2). The strongest observed effect from the cortical analyses in ADHD was in surface area, as cases showed a significant overall smaller surface area, compared to controls (Hoogman et al., 2019). This is in stark contrast to the ASD results, where no surface area affects were observed. The limitation of these analyses is the lack of full ASD symptomatology/diagnosis coverage in the ADHD cohorts and vice versa.

Based on these patterns of overlapping and unique effects in the separate analyses of the ADHD and ASD working groups, the next logical step was to repeat these analyses on the combined data from the two working groups. One of the main advantages of a mega-analytic approach based on common analysis pipelines in the different ENIGMA working groups is the comparability of the data. In a recent cross-disorder analysis, we combined structural brain data from the ENIGMA-ADHD, ENIGMA obsessive compulsive disorders (OCD), and ENIGMA-ASD working groups in order to investigate shared and unique effects among the three disorders (Boedhoe et al., 2019). The analysis included 2,271 subjects with ADHD, 1,771 with ASD, 2,323 with OCD, and 5,827 controls, and was subdivided by age into children (<12 years), adolescents (12–17 years), and adults (18 years and older). Findings showed strongest overlap between ASD and ADHD effects in childhood, where both cases with ADHD and ASD showed overall lower volumes in subcortical areas, as well as lower cortical thickness in precentral and temporal lobes. However, effect sizes were small, and most did not survive correction for multiple comparisons. When comparing cases among ADHD, ASD and OCD, we saw the largest difference in total ICV: children with ASD showed a higher average ICV, compared both to controls and with cases with ADHD or OCD. Hippocampal volumes were smaller in children with ADHD as compared with children with OCD, and smaller in adults with OCD and ASD as compared with controls, although neither this difference survived multiple comparison correction. As for cortical thickness, adults with ADHD had lower cortical thickness in orbitofrontal, inferior frontal and

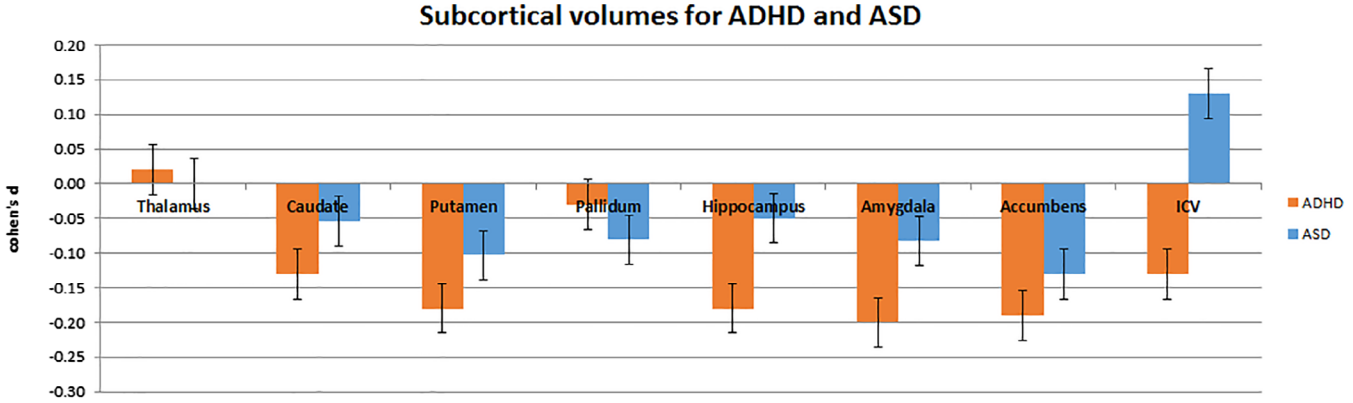

FIGURE 1 Cohen's d effect sizes for the subcortical volumes and total intracranial volume (ICV) for both ADHD and ASD cohorts as compared to controls. Figures taken and adapted from Hoogman et al. (2017) and van Rooij et al. (2018)

TABLE 1 Summary of findings of the (sub)cortical analyses in ENIGMA-ADHD and ENIGMA-ASD

Working group	Results of subcortical analyses	Results of cortical thickness analyses	Results of cortical surface area analyses	Additional findings
ENIGMA-ADHD	-smaller accumbens, amygdala, caudate nucleus, hippocampus, putamen and *intracranial volume* in all samples combined and when stratified only significant in children with ADHD. -with the exception of a significant smaller hippocampus volume in adolescents with ADHD	-thinner fusiform gyrus and *temporal pole* in all samples combined and when stratified into age groups, only significant in children with ADHD. -no differences in adolescents and adults with ADHD	-smaller surface areas for: superior frontal gyrus, lateral orbitofrontal cortex, posterior cingulate cortex, caudal middle frontal gyrus, middle temporal gyrus, and total surface area in children with ADHD. -no differences in adolescents and adults with ADHD	-siblings of individuals with ADHD showed smaller surface area for caudal middle frontal gyrus, superior frontal gyrus and total surface area. - children in the general population also showed higher rates of symptoms of inattention to correlate with surface area of the caudal middle frontal gyrus, the middle temporal gyrus and total surface area
ENIGMA-ASD	Cases with ASD showed smaller volume of the nucleus accumbens, amygdala, pallidum, and putamen and a *bigger intracranial volume*.	Cases with ASD showed greater cortical thickness in frontal brain areas (including the *frontal pole*), and lower cortical thickness in temporal/occipital brain areas (including the fusiform gyrus).	Cortical analysis showed no detectable differences in regional and total surface areas.	The effects of age were uniform over all subcortical and cortical findings—all showed a distinct peak difference between cases with ASD and controls around adolescence, and normalization in adults.

Note: Results that are underlined are overlapping results with the same direction of the effect for both disorders. Results in *italic* indicate overlapping regions affected for both disorders but with opposite effects.

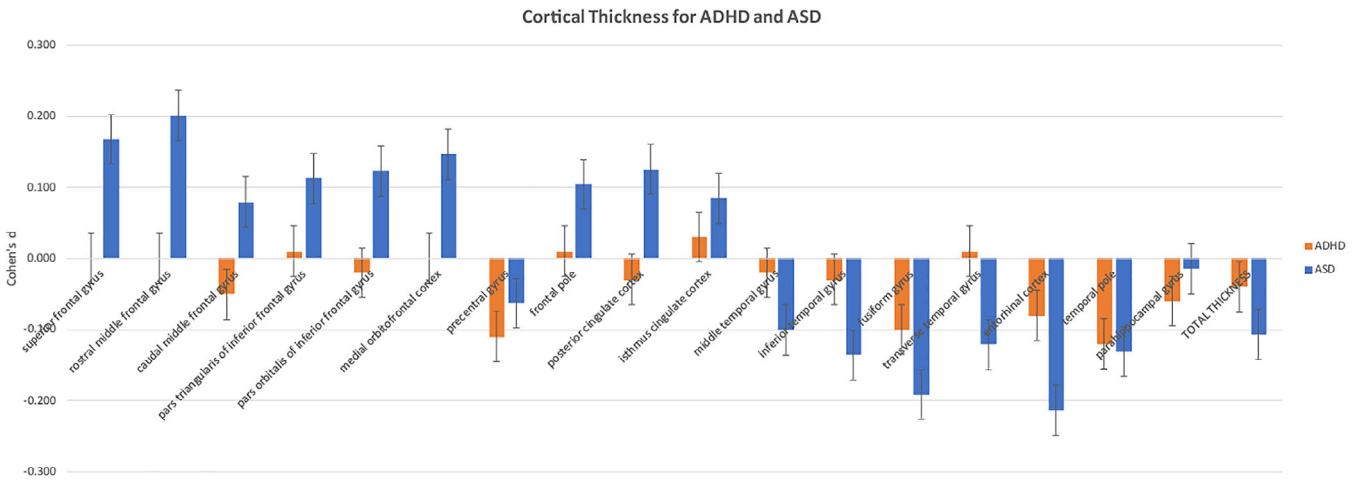

FIGURE 2 Cohen's *d* effect sizes for the cortical measures for both ADHD and ASD cohorts as compared to their controls. Figures taken and adapted from Hoogman et al. (2019) and van Rooij et al. (2018). Only the Freesurfer segmentations which showed a significant effect in either group are depicted, this means that only results of the thickness analyses are depicted here, as none of the surface area results were significant in the ASD analyses

cingulate areas, compared with adults with ASD, OCD and healthy controls. Taken together, these analyses indicated that there are unique cortical features in each disorder, but also considerable overlap between the two disorders, specifically when considering cortical thickness. Subcortical volumes were similarly affected in both ASD and ADHD, although the effects sizes over all age bins remained quite small.

4 | SECONDARY PROJECTS WITHIN ENIGMA-ADHD AND ENIGMA-ASD

In the spirit of ENIGMA, researchers within the collaboration are encouraged to perform additional analyses on the collected data aiming to address alternative research questions, or to use the network to test new analytic strategies and methods. For ENIGMA-

ADHD and ENIGMA-ASD, there are four projects with overlapping objectives. These are projects on laterality, machine learning, stratification, and virtual histology. Within ENIGMA-ADHD, an additional project focused on the cerebellum was also conducted. These projects are at various stages, and have been either published after peer review, posted as preprint without peer review on bioRxiv and awaiting peer review results, or are still in the process of being analyzed and written up. Table 2 outlines an overview each projects.

4.1 | Laterality analysis in ENIGMA-ADHD and ENIGMA-ASD

The laterality projects in the ADHD and ASD working groups aim to identify changes of left–right structural brain asymmetry in the affected populations. In contrast to previous findings in ADHD literature, the ENIGMA-ADHD laterality study showed no evidence for asymmetry in the caudate nucleus. All the other brain asymmetry analyses for case–control differences in children, adolescents and adults, showed no significant results that survived multiple comparison correction (Postema, Hoogman, et al., 2020). Alterations in the degree of cortical thickness asymmetry in frontal, cingulate, and inferior temporal areas were observed in the ENIGMA-ASD laterality study (Postema, van Rooij, et al., 2019), with subjects with ASD showing reduced asymmetry in all areas. The only exception to this was leftward putamen asymmetry, which was significantly increased in ASD.

4.2 | Machine learning results in ENIGMA-ADHD and ENIGMA-ASD

Both subcortical and cortical data were used to predict case–control status through machine learning within ENIGMA-ADHD (Zhang-James et al., 2019). Using support vector machine, random forests, K-Nearest Neighbors, and gradient boosting classifiers, the model was estimated in 85% of the sample while the remaining 15% of the sample was used to test the model's accuracy. Results showed a statistically significant discrimination between ADHD and control subjects. However, prediction accuracies were relatively low at 67% for adults and 66% for children. The most informative structures unsurprisingly overlapped with those structures that showed significant case–control differences in the main analysis of the ENIGMA-ADHD data: ICV, surface area, and some subcortical volumes (Hoogman et al., 2017; Hoogman et al., 2019). It is encouraging to see that by combining all brain data in the machine learning analysis, instead of examining isolated case–control differences, the adult group did show significant case–control differences. A model based on child data significantly predicted ADHD status in the adult sample and vice-versa, suggesting that the structural MRI differences detected by the machine learning algorithm were similar in children and adults. In order to increase the prediction, larger sample sizes or the addition of other data modalities (e.g., diffusion MRI, resting state functional MRI) might be required. Alternatively, this may also be achieved by integrating machine learning results with other cohorts, like ASD.

The same machine learning strategy has been applied in an ongoing study within the ASD working group. The analyses gave mostly similar results in terms of predictive accuracy, with a preliminary low accuracy of around 60%. However, a striking result occurred when merging the ENIGMA-ADHD and ASD cohorts in the training set. Preliminary results indicate that the predictive accuracy on the diagnosis of ASD in the prediction set was significantly higher when the training set includes also the ENIGMA-ADHD data. This may be partly due to the fact that in this case, the number of controls is doubled, however, it may also be due to the fact that learning examples of a third diagnostic category (in this case ADHD) may help the algorithm dissociate more clearly between the other two (ASD and controls). These preliminary findings demonstrate that, even though the effect sizes of brain differences on a group level are small, there is still much information in these morphometric features that advanced algorithms can use to dissociate cases from controls. Additionally, it highlights the importance of collaboration between scientists working on different disorders in neurodevelopmental research in general, and within the ENIGMA consortium in particular.

4.3 | Stratification analyses in ENIGMA-ADHD and ENIGMA-ASD

An important observation from the primary structural brain analyses published by both the ENIGMA-ADHD and -ASD working groups (Hoogman et al., 2017; Hoogman et al., 2019; van Rooij et al., 2018) was the high within-group variance in any given brain metric, which makes it hard to detect between-group differences. We hypothesize that, on a population level, different neuroanatomical profiles may exist, which would correspond to more homogeneous neuroanatomical subgroups. An important secondary goal of ENIGMA-ADHD and ENIGMA-ASD is therefore to stratify the structural brain data into subgroups, and investigate how this influences case–control comparisons and whether these subgroups have a unique neurobiological profile.

In order to investigate potential stratifications in the subcortical volumes, we employed a two-step analysis. First, the subcortical volumes for all subjects were entered in an exploratory factor analysis (EFA), which is used to summarize the nine subcortical volumes into a couple of underlying factors. Next, these factors were used in a Community Detection clustering analysis, to see if there were specific subgroups within the patient and control populations that differ in their subcortical brain profile (Li et al., 2019). In an ongoing study, similar analyses are being carried out for both the ENIGMA-ADHD and ASD datasets.

The EFA results showed that variations in subcortical volumes can be reduced to three main factors, in males aligning with the striatum, limbic system, and thalamus. This factor structure was based on both cases and controls, and was stable between the ADHD and ASD cohorts. There were some differences between

TABLE 2 Overview of the published and ongoing work by the ENIGMA-ADHD and ASD working groups

Reference	Title	Working group	Status	Doi
Hoogman et al. (2017)	Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis.	ADHD	Peer reviewed and published	https://doi.org/10.1016/S2215-0366(17)30049-4
van Rooij et al. (2018)	Cortical and subcortical brain morphometry differences between patients with autism spectrum disorder and healthy individuals across the lifespan: Results from the ENIGMA ASD Working Group.	ASD	Peer reviewed and published	https://doi.org/10.1176/appi.ajp.2017.17010100
Shaw et al. (2018)	A multicohort, longitudinal study of cerebellar development in attention deficit hyperactivity disorder.	ADHD	Peer reviewed and published	https://doi.org/10.1111/jcpp.12920
Hoogman et al. (2019)	Brain imaging of the cortex in ADHD: A coordinated analysis of large-scale clinical and population-based samples.	ADHD	Peer reviewed and published	https://doi.org/10.1176/appi.ajp.2019.18091033
Postema, van Rooij, et al. (2019)	Altered structural brain asymmetry in autism spectrum disorder in a study of 54 datasets.	ASD	Peer reviewed and published	https://doi.org/10.1038/s41467-019-13005-8
Zhang-James et al. (2019)	Machine learning classification of attention-deficit/hyperactivity disorder using structural MRI data.	ADHD	Under review, published on bioRxiv	https://doi.org/10.1101/546671
Boedhoe et al. (2019)	Subcortical brain volume, regional cortical thickness and cortical surface area across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive–compulsive disorder (OCD).	ADHD & ASD (and OCD)	Accepted for publication at AM. J.Psy, published on bioRxiv	https://doi.org/10.1101/673012
Li et al. (2019)	Characterizing neuroanatomic heterogeneity in people with and without ADHD based on subcortical brain volumes.	ADHD	Under review, published on bioRxiv	https://doi.org/10.1101/868414
Postema et al. (2020)	An ENIGMA consortium analysis of structural brain asymmetries in attention-deficit/hyperactivity disorder in 39 datasets.	ADHD	Under review, published on bioRxiv	https://doi.org/10.1101/2020.03.03.974758
Patel et al. (2020)	Virtual histology of cortical thickness reveals shared neurobiology underlying six psychiatric disorders: A meta-analysis of 148 cohorts from the ENIGMA Consortium.	ADHD & ASD (and other working groups)	Not peer reviewed, submitted	NA
Zhang-James et al. (2020)	Improved classification performance with autoencoder-based feature extraction using cross-disorder datasets.	ADHD and ASD	In preparation	NA
Li et al. (2020)	Dissecting the heterogeneous subcortical brain volume of autism spectrum disorder (ASD) using community detection.	ASD	In preparation	NA

Abbreviation: NA, not available.

males and females, and among female children, adolescents, and adults. Community detection analysis indicated that the cohorts can subsequently be stratified into four separate profiles, each corresponding to a unique loading pattern on the striatum, limbic system, and thalamus factors. Once more, these observed communities were stable between the ADHD and ASD analyses, and the distribution between the communities was comparable between cases and controls. This allowed us to then look at case–control differences within each of the four communities. The effect sizes of the case–control comparisons for both ADHD and ASD were significantly higher within the four distinct communities than they were over the entire cohort. This study also indicated that the community structure may change over the lifespan, with one community disappearing in adulthood. This shift suggests that neuroanatomical diversity may decrease with age. As of now, both the ADHD and ASD cohorts had too few females to conduct sufficiently powered community detection analyses accounting for sex, as sex differences in neuroanatomical organization are a highly important topic within ADHD and ASD research. We hope that with further growth of the ENIGMA cohorts, these analyses may soon become feasible.

Although all the findings discussed here are still preliminary at the time of writing, all results support our main hypothesis, which is that it is likely that there are relatively more homogeneous subgroups within the population based on brain structure, and that taking into account these subgroups can significantly increase the effect sizes of our case–control analyses.

4.4 | Virtual histology analyses for ENIGMA-ADHD and ENIGMA-ASD and four other disease working groups

Neuroimaging studies have observed robust differences in cerebral cortical morphology (thickness and surface area) within patients across different psychiatric disorders (Thompson et al., 2020). However, the neurobiological changes underlying these macroscopic structural differences in the cerebral cortex are not well understood. To gain further insights into the profiles of group differences in the ENIGMA-ADHD and ENIGMA-ASD cohorts, we employed a virtual histology approach (Patel et al., 2018; Shin et al., 2018). This entails relating inter-regional profiles of gene expression from the Allen Human Brain Atlas with inter-regional profiles in differences of cortical thickness across the 34 regions of the Desikan-Killiany atlas (Desikan et al., 2006; Hawrylycz et al., 2012). Virtual histology may allow us to make inferences about which cell types (e.g., pyramidal, interneuron, astrocytes, microglia, and oligodendrocyte) are enriched in regions that show large group differences in cortical thickness. The aim for virtual histology projects is to employ this approach in six psychiatric disorders (ADHD, ASD, bipolar disorder, OCD, major depressive disorder, and schizophrenia) in order to characterize shared and/or unique neurobiology of group differences in cortical thickness across these disorders; a total of 12,006 cases and 14,842 controls are contributing to this project, which is currently ongoing.

4.5 | Cerebellum analysis in ENIGMA-ADHD

One additional project in ENIGMA-ADHD aimed to investigate the specific neuroanatomy of the cerebellum in ADHD. A collaborative initiative of four cohorts from the working group (Shaw et al., 2018) segmented various regions in the cerebellum to identify growth trajectories in these regions for cases and controls. In a sample of 1,656 subjects (patients and controls), diagnostic differences in growth in the corpus medullare (cerebellar white matter) emerged. Specifically, cases with ADHD showed slower growth in early childhood compared to the typically developing group and a reversed effect in late childhood.

5 | STRENGTHS, CHALLENGES, AND LIMITATIONS OF ENIGMA-ADHD AND ENIGMA-ASD

The main strength of the ENIGMA consortium in the field of ADHD and ASD brain imaging has been the sharing of existing data, which consequently further unifies the experience and expertise of the field. By going beyond meta-analyses and really sharing individual test statistics, we were able to run more sophisticated analyses than would have otherwise been possible.

The ENIGMA working groups have clear data management, writing, and publication guidelines described in a memorandum of understanding which is signed by all participating members. This ensures transparency among all working group members in both the process and the outcome of all new analyses. The open nature of the working groups has a positive snowballing effect of new sites and PI's joining regularly, thus resulting in a larger body of data for each new analysis. The ENIGMA policy on secondary proposals dictates that all working group members can submit secondary proposals, which has led to many interesting and important contributions which were spearheaded by different members of the ENIGMA-ADHD and ASD working groups. As highlighted previously, another strength is the sharing of open access protocols for imaging analyses, developed by dedicated methods working groups within the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols/). These detailed protocols include brain segmentation into defined anatomical regions using FreeSurfer 5.3 and quality control procedures, and help remove variance that would come from using different methods. In general, the statistical models that are used to calculate case–control differences are also similar among working groups. Mixed linear models using the nlme package in R are implemented with age, sex and case–control status as fixed variables and “site” as a random factor. Varying among working groups, interactions of the fixed factors are sometimes added to the model to acquire a better model fit. This varies

among the working groups. Depending on the brain measures analyzed, additional covariates accounting for global head size are added. In subcortical volume projects intra cranial volume was added as covariate, and in cortical surface area projects, analyses were performed with and without total surface area as covariate.

Even with these efforts, several challenges and limitations remain. One of the key difficulties that the working groups face is the nature of the data itself. Legacy data, which refers to the pre-existing data from previous studies and publications, inherently lacks harmonization of data collection and phenotyping protocols, and is additionally less accessible for follow up data acquisition than in new studies. It has at times proven difficult to repeatedly organize new analyses which require access to the locally stored raw imaging data, especially at sites where the authors of the original publications have left and moved to new positions. Similarly, demographic and phenotypic data from the many different sites were acquired in different years across several decades, using different tools and methods, with different goals in mind. This led to considerable heterogeneity in, for instance, the symptom ratings within cohorts, as well as inconsistent assessment of comorbidities. In ENIGMA-ADHD, we currently have information available for 55% of the patients on ADHD symptom rating scales. For 58% of the patients there is information about comorbidities and for 44% and 66% of the patients we have data available for lifetime stimulant use and current stimulant use, respectively. For ENIGMA-ASD, the Autism Diagnostic Observation Scale (ADOS) is available for 27% of the cohort, as well as 15% for comorbidity information and 49% for current medication use. The historical focus of existing publications on a categorical (case, control) rather than dimensional phenotyping approach limits the depth of phenotype associations available in ENIGMA-ADHD and ASD. Another example of the difficulties that we face can be found in the change from DSM-IV to DSM-5. Before DSM-5 was published, ADHD and ASD could not be diagnosed simultaneously. This led many older samples to forgo acquiring ADHD/ASD comorbidity data, as this was thought to be superfluous at the time. Given that there likely was some comorbidity of ASD symptoms in the ADHD cohort and vice versa, this may have increased the overlap in structural brain alterations between the two cohorts. Re-contacting the original patients or even researchers of these legacy samples is often not feasible, limiting depth and fidelity of the available phenotypic data in the ENIGMA-ADHD and ASD cohorts.

6 | FOLLOW-UP OF ENIGMA-ADHD AND ENIGMA-ASD: RESULTS BEYOND THE COLLABORATION

Work from the ENIGMA-ADHD and ENIGMA-ASD groups has inspired various follow-up analyses. The ENIGMA-ADHD working group discovered volume reductions in patients with ADHD in ICV and volumes of subcortical regions. However, how such alterations contribute to the disease phenotype remains largely unknown. As both ADHD and brain volumes have a high heritability, it has been suggested that genetic variants underlying ADHD pathophysiology may also influence brain volume variation. A recent study investigated the genetic covariance between ADHD risk and the brain volumes implicated in ADHD. On a global, genome-wide level a significant negative genetic correlation between ADHD and ICV was found, meaning that variants linked to smaller ICV were associated with increased ADHD risk (Klein et al., 2019). This resembles the phenotypic observation that individuals with ADHD have smaller ICV relative to control subjects. On the single variant and gene-wide levels, several significant loci were associated with both ADHD risk and brain volume (Klein et al., 2019). Similar genetic overlap analyses revealed that cortical structure variation is genetically correlated with ADHD (Grasby et al., 2020). More specifically, a significant negative genetic correlation between ADHD and global surface area, a brain phenotype highly correlated with ICV, was found (Grasby et al., 2020). This type of integrated genome-wide analyses can help develop new hypotheses about biological mechanisms by which brain structure alterations may be involved in ADHD disease etiology. The genetic correlation between ADHD and ICV showed some specificity to this disorder, as it was not found in studies of other psychiatric disorders, such as schizophrenia (Adams et al., 2016; Franke et al., 2016), major depressive disorder (Wigmore et al., 2017), or ASD (Grove et al., 2019), using similar methods. A related analysis by Radonijc et al., 2020 (this issue) showed that, across several disorders investigated by ENIGMA working groups, those that showed greater case–control structural brain differences also showed more similarities in their common genetic variant architectures.

In analyses using the case–control standardized mean differences for subcortical regions from the ADHD-ENIGMA analyses, Hess and coworkers (Hess, Akutagava-Martins, Patak, Glatt, & Faraone, 2018) reported that gene expression profiles (Allen Human Brain Atlas) for three biological pathways were significantly correlated with ADHD-associated volumetric reductions: apoptosis, oxidative stress, and autophagy. These correlations were strong and significant in children with ADHD, but not in adults. In a subsequent analysis that also included cortical data from ENIGMA-ADHD, the same group found that ADHD-associated volumetric reductions were associated with apoptosis, autophagy, and neurodevelopment gene pathways and with regional abundances of dopaminergic neurons, astrocytes, oligodendrocytes, and neural progenitor cells (Hess, Radonjić, Patak, Glatt, & Faraone, 2019). These data suggest that the selective brain region vulnerability seen in ADHD may be due to differences in the cellular composition and constitutive gene expression between regions, which do and do not show ADHD-associated volumetric changes.

7 | THE FUTURE FOR COLLABORATIVE NEUROIMAGING IN ADHD AND ASD

Great strides have been made toward fulfilling the aims of the ENIGMA collaboration, especially for increasing the power of neuroimaging studies in ADHD and ASD. The published work of these collaborations includes by far the biggest sample sizes in the field of

neuroimaging for the respective disorders. First, this has made it possible to identify robust case–control differences with stringent methods (such as split half validation, Mackey et al., 2018). Second, although we need to be aware of the limitations of cross-sectional data, the wide age range of our samples (ADHD: 4–63 years, ASD: 2–64 years) allows the examination of case–control differences across the life-span. Together with the large sample sizes that facilitate powerful age-group analysis, we can formulate more specific hypotheses about the development of brain differences across the life-span. Third, the additional projects derived from these collaborations are strong examples that our aim of combining expertise to boost our understanding of ADHD and ASD in relation to the brain has been met and is continuously replenished with new ideas. Not only within the collaborative group itself, but also other researchers have also been inspired to come up with subsequent research questions to generate even more knowledge about brain differences that are associated with the disorders, coming from related fields (Hess et al., 2018; Klein et al., 2019). While the first articles of additional analyses are now being published, much work is still ongoing, and more cohorts are still joining our working groups. We therefore expect more output from these initiatives. Finally, we aimed to reduce methodological heterogeneity by making the preprocessing and analysis pipeline used in ENIGMA-ADHD and ASD public, as well as many of the analysis results per site. This gives unprecedented insights into the amount and range of variance of outcomes between studies that for the first time establishes a clear baseline against which new samples can easily be compared.

7.1 | Collecting additional data within our working groups

Our future work will be dedicated to performing new analyses and including additional data. The ENIGMA-ADHD and -ASD groups are currently working on the analysis of structural connectivity data from diffusion tensor imaging (DTI). With the DTI projects we will perform similar analyses as for brain volume but move beyond testing for isolated brain regions. Here we can, again, make use of processing pipelines provided by ENIGMA, which have already been successfully used (Favre et al., 2019; van Velzen et al., 2019; Villalón-Reina et al., 2019). Within the ENIGMA-ASD cohort, resting state fMRI data are also being analyzed, pooled together with existing datasets such as the EU-AIMS cohort, parcellated into standard functional regions of interest, and used for a graph-theory analysis of the functional brain (dis)connectivity. The addition of DTI and resting state fMRI data to the existing structural brain data in the ENIGMA-ADHD and ASD working groups is an important step toward true multimodal imaging data integration, one of the most important long-term goals of these ENIGMA working groups. All our current findings, as well as the literature on ADHD and ASD, overwhelmingly indicate that neural alterations are visible across all available imaging modalities. There currently exist no large-scale dataset where structural, functional, and connectivity data are combined, so it is largely unclear how findings among these different modalities are interrelated. To move toward a more complete neurobiological model of ADHD and ASD, multimodal data integration will be key.

To learn more about the overlap and differences between ADHD and ASD, we want to focus on samples that have allowed dual diagnosis of both disorders. As was discussed in the strengths, challenges and limitations section, most of the current studies into ADHD/ASD excluded the other disorder for data collection. Adding a third group with a true combined diagnosis will strengthen the cross-disorder analysis of ADHD and ASD immensely, and will aid the investigation of how the genetic and neural correlates of ADHD and ASD interact, and how this influences the development of the disease phenotype over the lifespan.

7.2 | Collaborating with other consortia

As was mentioned in this article, ADHD and ASD may be seen as different manifestations of a broader phenotype. This view can be further extended to include multiple neurodevelopmental disorders, most notably OCD and Tourette's syndrome. A large overlap in comorbidity between these disorders as well as in the cognitive and neural alterations, lead to the hypothesis that the standard categorical disease classification for neurodevelopmental disorders may need to be revisited, and that ADHD, ASD, OCD, and Tourette's syndrome might actually lie on an impulsivity-compulsivity continuum, sharing overlapping etiologies that converge in dysfunctional brain circuitries (Clark, Cuthbert, Lewis-Fernández, Narrow, & Reed, 2017; Huisman-van Dijk, van de Schoot, Rijkeboer, Mathews, & Cath, 2016). A major next step in the ENIGMA consortium is the aim to unite multimodal imaging comparisons across the neurodevelopmental disorder working groups, not only for ADHD and ASD, but also including ENIGMA-OCD and Tourette's syndrome.

Additionally, for both ADHD and ASD it would be of great interest to combine brain data from longitudinal samples. The previously reported delay of maturation in ADHD, the absence of case–control differences in the adult sub-analysis in ENIGMA-ADHD, or the changes restricted to adolescence in ASD and the changes in the presentation of the disorders all support looking more closely and with better data at the life-span perspective of brain changes related to ADHD. Early biomarkers associated with ASD's development and treatment outcome would additionally be of tremendous value to the clinical community. Currently, and to this end, medium scale multicenter longitudinal data are being collected as part of the EU-AIMS project (Murphy & Spooren, 2012), which may offer a potential collaboration partner for ENIGMA-ASD to investigate both longitudinal structural brain analysis, but also includes extensive behavioral phenotyping as well as EEG and eye-tracking data, which offers new opportunities to link the ENIGMA imaging findings to a wider set of behavioral and biological metrics.

The behaviors which are associated with both ADHD and ASD are not unique to just a patient population, but exist as continuous traits within the general population (Asherson & Trzaskowski, 2015;

Bralten et al., 2018). This means that both the genetic and neuroimaging features which are linked to ADHD and ASD may also be found as distributed traits in population samples. Combining the results of the ENIGMA analysis and the analysis of population-based brain data have been successful in the case of ADHD cortical analyses (Hoogman et al., 2019). We want to expand these types of analyses because it gives us a better picture of brain characteristics across the whole spectrum of these psychiatric traits.

Lastly, to combine genetic and neuroimaging data within ENIGMA-ADHD and ASD, ideally one would need genetic and imaging data from the same subjects to investigate which genetic factors contribute to the brain characteristics that have been found. Unfortunately, the samples in ENIGMA-ADHD and ASD are still too small to conduct such analyses. However, combining data from multiple large-scale databases of other collaborations has shown that this also delivers new information, for example the project about the genetic overlap of ADHD risk and genetic factors involved in ADHD related brain volumes (Klein et al., 2019). In the future we aim to perform more of these types of analyses and encourage and invite other researchers to come up with interesting hypotheses.

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CONFLICT OF INTEREST

Paul M. Thompson was supported in part by a research grant from Biogen, Inc. (Boston, USA) for research unrelated to this manuscript. *Odile A. van den Heuvel* received speaker honorarium from Benecke. *David Coghill* served in an advisory or consultancy role for Lilly, Medice, Novartis, Oxford outcomes, Shire and Viforpharma. He received conference support or speaker's fee by Janssen McNeil, Lilly, Medice, Novartis, Shire and Sunovian. He is/has been involved in clinical trials conducted by Lilly & Shire. The present work is unrelated to the above grants and relationships. *Jonna Kuntsi* has given talks at educational events sponsored by and Medicine; all funds are received by King's College London and used for studies of ADHD. *Paulo Mattos* was on the speakers' bureau and/or acted as consultant for Janssen-Cilag, Novartis, and Shire in the previous 5 years; he also received travel awards to participate in scientific meetings from those companies. The ADHD outpatient program (Grupo de Estudos do Déficit de Atenção/Institute of Psychiatry) chaired by Dr. Mattos has also received research support from Novartis and Shire.The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. *Tobias Banaschewski* served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Shire, and Infectopharm. He received conference support or speaker's fee by Lilly, Medice, and Shire. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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