Meta-analysis of Gray Matter Abnormalities in Autism Spectrum Disorder

Should Asperger Disorder Be Subsumed Under a Broader Umbrella of Autistic Spectrum Disorder?

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Context: Studies investigating abnormalities of regional gray matter volume in autism spectrum disorder (ASD) have yielded contradictory results. It is unclear whether the current subtyping of ASD into autistic disorder and Asperger disorder is neurobiologically valid.

Objectives: To conduct a quantitative meta-analysis of voxel-based morphometry studies exploring gray matter volume abnormalities in ASD, to examine potential neurobiological differences among ASD subtypes, and to create an online database to facilitate replication and further analyses by other researchers.

Data Sources: We retrieved studies from PubMed, ScienceDirect, Scopus, and Web of Knowledge databases between June 3, 1999, the date of the first voxel-based morphometry study in ASD, and October 31, 2010. Studies were also retrieved from reference lists and review articles. We contacted authors soliciting additional data.

Study Selection: Twenty-four data sets met inclusion criteria, comprising 496 participants with ASD and 471 healthy control individuals.

Data Extraction: Peak coordinates of clusters of regional gray matter differences between participants with ASD and controls, as well as demographic, clinical, and methodologic variables, were extracted from each study or obtained from the authors.

Data Synthesis: No differences in overall gray matter volume were found between participants with ASD and healthy controls. Participants with ASD were found to have robust decreases of gray matter volume in the bilateral amygdala-hippocampus complex and the bilateral precuneus. A small increase of gray matter volume in the middle-inferior frontal gyrus was also found. No significant differences in overall or regional gray matter volumes were found between autistic disorder and Asperger disorder. Decreases of gray matter volume in the right precuneus were statistically higher in adults than in adolescents with ASD.

Conclusions: These results confirm the crucial involvement of structures linked to social cognition in ASD. The absence of significant differences between ASD subtypes may have important nosologic implications for the *DSM-5*. The publically available database will be a useful resource for future research.

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AUTISM IS A DEVELOPMENTAL disorder characterized by deficits in communication and reciprocal social interaction and a restricted, repetitive, or stereotyped pattern of behaviors, interests, and activities evident by the age of 3 years.[1] Autism spectrum disorder (ASD) is currently used as a broad umbrella term that includes a wide range of clinical presentations, including autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified.[1] A recent study[2] estimates the prevalence of ASD to be 1% in children aged 9 to 10 years, with approximately 60% of those having associated intellectual disability.

The causes of ASD are still to be fully elucidated, although it is known to have a strong genetic component.[3] It is also thought to result from maturation-related changes in various brain systems. One of the most well-replicated findings in ASD is the increased total head size and brain volume.[4,5] This is mainly due to increased volumes in the frontal lobes and anterior temporal regions, most notably in the preschool years.[6]

Modern neuroimaging methods such as magnetic resonance imaging have provided important insights into the neurobiological basis for ASD.[7] Abnormalities in brain regions known to be important for verbal and nonverbal communication, social interaction, and executive functions, as well as related white matter tracts, have been reported.[7,8] However, the results of these studies have been less consistent than

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expected. For example, volume increases and decreases have been reported in the amygdala, a region hypothesized to be critically involved in ASD.[7,9-11] These inconsistencies might exist partially because of the clinical and etiologic heterogeneity of the disorder,[12] as well as methodologic aspects of the studies, such as the use of manual or semiautomated region of interest (ROI) methods, which focus on a priori selected regions, thus precluding the exploration of other brain regions potentially implicated in ASD.

Fully automated, whole-brain voxel-based morphometry (VBM) methods,[13,14] which overcome some of the limitations of the ROI approach, provide a potentially powerful and unbiased tool to study the neural substrates of ASD. Since the advent of VBM methods, an increasing number of studies have applied them to the study of ASD, but their results have also been relatively inconsistent. These studies are often limited by relatively small sample sizes, resulting in insufficient statistical power. Voxel-based meta-analytical methods are ideal to quantify the reproducibility of neuroimaging findings and to generate insights difficult to observe in isolated studies.[15,16]

In this study, we searched all known published and unpublished VBM studies of gray matter in ASD and applied novel voxel-based meta-analytical methods to establish the most consistently reported abnormalities in this disorder, without the constraints of a priori hypotheses. We also examined potential differences in gray matter volume between the main subtypes of ASD, namely, autistic disorder and Asperger disorder, which remains an important nosologic issue in the *DSM-5*.[17] Specifically, draft criteria for the *DSM-5* have proposed merging Asperger disorder into ASD because of the lack of solid empirical data distinguishing Asperger and high-functioning autism subgroups with regard to cause, course, and neurocognitive profile.[18-20] Finally, to facilitate replication and further analyses by research groups internationally, we have also developed a readily accessible online database containing all the data and methodologic details from every study included in this meta-analysis.

METHODS

SEARCH AND INCLUSION OF STUDIES

A literature search of articles, posters, and abstracts published from June 3, 1999, the date of the first VBM study in ASD,[21] through October 31, 2010, was conducted using the PubMed, ScienceDirect, Scopus, and Web of Knowledge databases. The search keywords were *autism* or *Asperger* plus *morphometry*, *voxel based,* or *voxelwise*. In addition, manual searches were conducted among the reference sections of the retrieved studies and several review studies. Any work comparing individuals with autistic disorder or Asperger disorder with healthy control individuals by means of whole-brain VBM was considered for inclusion in the meta-analysis. Studies containing duplicated data sets (ie, analyzing at least half of the sample in different works) and studies with fewer than 9 participants in the ASD group were excluded.

DATA EXTRACTION

Data from included studies were extracted by 2 of us (E.V. and J.R.) and then compared to minimize interpretation and data entry errors. In all but 2 studies, the corresponding authors were contacted via e-mail to obtain data not included in the original works. Meta-analysis of Observational Studies in Epidemiology guidelines[22] were followed in the study.

GLOBAL DIFFERENCES IN GRAY MATTER VOLUME

Meta-analytical differences in global gray matter volumes between participants with ASD and controls were assessed using random-effects models with the Globals procedure in Signed Differential Mapping (SDM),[23] which uses restricted maximum-likelihood estimation, a fitting method that has been recommended instead of previous ones for its optimal balance between lack of bias and efficiency.[24]

REGIONAL DIFFERENCES IN GRAY MATTER VOLUME

Regional differences in gray matter volume between participants with ASD and controls were analyzed using SDM,[23] a novel voxel-based meta-analytic approach that is based on and improves on other existing methods.[25,26] The method has been described in detail elsewhere[27,28] and is briefly summarized herein.

First, SDM applies a strict selection of the reported peak coordinates of gray matter differences by only including those that appear statistically significant at the whole-brain level, preferably corrected for multiple comparisons. This practice is intended to avoid biases toward liberally thresholded brain regions because it is not uncommon in neuroimaging studies that the statistical threshold for some ROIs is more liberal than for the rest of the brain. Second, a map of the differences in gray matter is separately recreated for each study. This includes limiting voxel values to a maximum to avoid biases toward studies reporting various coordinates in close proximity and reconstructing increases and decreases of gray matter in the same map. Finally, the mean map is obtained by voxel-based calculation of the mean of the study maps, weighted by the squared root of the sample size of each study so that studies with large sample sizes contribute proportionally more to the final map. The statistical significance of each voxel is assessed by standard randomization tests.[27]

The main analysis reported herein was complemented by several additional analyses to assess the robustness and replicability of the findings,[27] namely, jackknife sensitivity analyses and descriptive analyses of quartiles. The jackknife sensitivity analysis consists of iteratively repeating the same analyses excluding 1 data set at a time to establish whether the results remain significant. The analyses of quartiles describe the proportion of studies reporting changes in a particular region (ie, 25%, 50%, or 75%), regardless of *P* values.[27,28]

EFFECTS OF ASD SUBTYPE AND AGE ON GLOBAL AND REGIONAL GRAY MATTER VOLUMES

Using recently developed methods,[28] we next regressed the global and regional gray matter differences between participants with ASD and controls from each study by ASD subtype (autistic vs Asperger disorder) and age (adult vs adolescent samples). Considering that some studies included participants with autistic disorder and participants with Asperger disorder, the diagnosis factor was coded as the percentage of participants with Asperger disorder.

The analysis of covariance (ANCOVA) of global gray matter differences returned a Q statistic (similar to an *F* statistic) that summarized the effects of diagnosis and age, a *z* statistic

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for the difference between participants with autistic disorder and participants with Asperger disorder, and a z statistic for the difference between adolescent and adult participants with ASD. Similarly, the ANCOVA of regional gray matter differences returned a map of the regional Q statistic, a map of the gray matter volume differences between participants with autistic disorder and participants with Asperger disorder, and a separate map of the differences between adolescent and adult participants with ASD. To minimize spurious findings, this ANCOVA was limited to the brain regions with significant differences between patients and controls in the main analysis.

RESULTS

INCLUDED STUDIES AND SAMPLE CHARACTERISTICS

As shown in **Figure 1**, the search retrieved 26 potentially suitable studies. Of those studies, 1 was excluded because it included fewer than 9 participants with ASD,[29] 1 was excluded because of a duplicated data set,[30] and 3 additional studies were excluded because of incompatible methods (ie, bilateral VBM[31,32]—a new statistical VBM approach to identify only bilateral abnormalities in the autistic brain—and single-case analysis[33]). One further study[34] had to be excluded because it was missing information that was key for our meta-analysis (ie, peak coordinates from whole-brain analysis).

After contacting the authors, no methodologic ambiguities remained regarding the design or results of the remaining 20 studies. Therefore, 20 studies could be included in this meta-analysis, comprising 24 independent data sets (that is, comparisons between groups of participants with ASD and healthy controls). Note that some studies included more than 1 sample of participants (or data sets). Nineteen of these studies were published or accepted for publication, and 1 was an unpublished analysis within an abstract. Ten studies included adult ASD samples[21,35-43] and another 10 studies included adolescent ASD samples.[44-53]

The included studies comprised 496 participants with ASD and 471 healthy controls. Among them, 452 were adults (228 controls: mean [SD] age, 27 [9.7] years; 224 ASD patients: mean [SD] age, 28 [10.1] years, 46.4% with autistic disorder, 52.2% with Asperger disorder, 1.3% unspecified) and 515 were adolescents (243 controls: mean [SD] age, 12 [4.3] years; 272 ASD patients: mean [SD] age, 13 [4.6] years, 69.5% with autistic disorder, 19.1% with Asperger disorder, 11.4% unspecified). The ASD diagnosis was established by means of the Autism Diagnostic Interview–Revised[54] in 17 studies and using *DSM-IV* criteria in the remaining 3 studies.[21,38,45] As indicated in **Table 1**, no relevant differences between participants with ASD and healthy controls were found in terms of sex, age, handedness, or IQ, reflecting the group matching used in the original studies. With the exception of 1 study,[44] the mean IQ of the participants was greater than 70. The IQ was not reported in 3 studies.[21,45,50] Only 1 study[35] included a completely female sample. Most of the studies (75.0%) specified that neurologic or psychiatric conditions were excluded, and only 12 participants with ASD (2.4%) were known to have comorbid conditions in 2 studies.[45,46] Medication use was not often reported; across all included studies, 24 participants with ASD (4.8%) were said to be taking medication at the time of scan. More clinical and methodologic details of each of the studies can be found at http://www.sdmproject.com/database/.

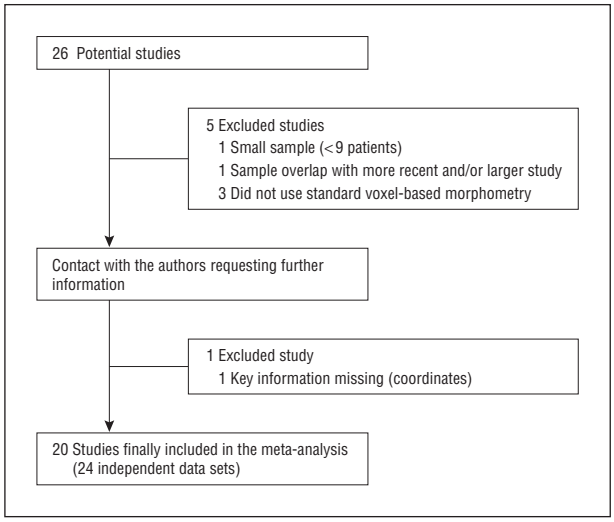

Figure 1. Inclusion of studies in the meta-analysis.

GLOBAL DIFFERENCES IN GRAY MATTER VOLUME

Global gray matter volume could be retrieved from 12 studies.* No statistically significant differences in global gray matter volumes were found between participants with ASD (n=312) and healthy controls (n=334) (unbiased Hedges[54,55] d=0.006, z=0.065, P=.95).

REGIONAL DIFFERENCES IN GRAY MATTER VOLUME

Data for this analysis were obtained from all 24 data sets. As indicated in **Table 2** and **Figure 2**, participants with ASD were characterized by a significant reduction of gray matter volume in the amygdala-hippocampus complex (particularly on the right side), extending to the right claustrum. Significant reductions in gray matter volume were also found in the bilateral medial parietal cortex (precuneus, Brodmann area [BA] 7), particularly on the right side, which extended to adjacent right-sided areas: superior parietal lobule, subgyral parietal lobe, and postcentral gyrus (BA7, BA40, and BA5). Finally, a small increase in gray matter volume was found in the left middle frontal gyrus extending to the inferior frontal gyrus (BA46 and BA10).

Replicability of these results was further assessed by a jackknife sensitivity analysis consisting of the systematic exclusion of 1 study at a time. As indicated in **Table 3**, the main results were highly replicable, especially for the right amygdala-hippocampus complex, which remained significant in all the combinations of data sets. The left amygdala-hippocampus complex remained significant in all but 2 combinations of studies.

**References 35-38, 40, 43, 46, 47, 49, 51-53.*

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Table 1. Detailed Demographic and Clinical Characteristics of the 24 Data Sets Included in the Meta-analysis

	Individuals With Autism						Healthy Control Individuals			
Source	No.	Age, Mean (SD), y	Males, %	Total IQ, Mean (SD)	Asperger Disorder, %	Autistic Disorder, %	No.	Age, Mean (SD), y	Males, %	Total IQ, Mean (SD)
Pediatric/adolescent samples										
Boddaert et al,[44] 2004	21	9.30 (2.20)	76	41.90 (21.30)	0	100	12	10.80 (2.70)	58	NA
Bonilha et al,[45] 2008	12	12.40 (4.00)	100	NA	0	100	16	13.20 (5.00)	100	NA
Brieber et al,[46] 2007	15	14.20 (1.90)	100	106.80 (21.40)	87	13	15	13.30 (1.80)	100	107.70 (12.70)
Freitag et al,[47] 2008	15	17.60 (3.60)	87	101.20 (21.20)	NA	NA	15	18.60 (1.20)	87	112.10 (18.00)
Hardan et al,[48] 2003	...	...	...	...	...	...	12	16.50 (8.20)	NA	109.50 (15.80)
Asperger disorder sample	12	16.40 (8.00)	NA	108.80 (13.50)	100	0	...	...	...	...
Autistic disorder sample	12	16.40 (8.20)	NA	113.40 (12.90)	0	100	...	...	...	...
Ke et al,[49] 2008	17	8.88 (1.96)	82	108.76 (19.07)	0	100	15	9.73 (1.67)	80	109.80 (19.22)
Kwon et al,[50] 2004	...	...	...	...	...	...	13	13.60 (3.10)	100	NA
Asperger disorder sample	11	13.50 (2.40)	100	NA	100	0	...	...	...	...
Autistic disorder sample	9	14.00 (3.30)	100	NA	0	100	...	...	...	...
Langen et al,[51] 2009	99	12.89 (4.45)	92	107.59 (13.56)	0	100	89	12.36 (4.79)	92	109.99 (12.81)
McAlonan et al,[52] 2008	...	...	...	...	...	...	55	10.70 (2.74)	85	>70
Asperger disorder sample	16	11.70 (2.78)	81	>70	100	0	...	...	...	...
Autistic disorder sample	17	11.40 (2.48)	82	>70	0	100	...	...	...	...
Waiter et al,[53] 2004	16	15.40 (2.24)	100	100.40 (21.70)	NA	NA	16	15.50 (1.60)	100	99.70 (18.30)
Adult samples										
Abell et al,[21] 1999	15	28.75 (6.60)	80	NA	100	0	15	25.33 (3.10)	80	NA
Craig et al,[35] 2007	14	37.90 (11.40)	0	103.40 (17.00)	71	29	19	35.00 (14.00)	0	111.20 (14.50)
Ecker et al,[36] 2010	22	27.00 (7.00)	100	104.00 (15.00)	59[a]	27[a]	22	28.00 (7.00)	100	111.00 (10.00)
Hyde et al,[37] 2010	15	22.70 (6.40)	100	100.40 (12.60)	0	100	15	19.20 (5.00)	100	106.60 (12.10)
Kosaka et al,[38] 2010	32	23.80 (4.20)	100	101.60 (15.60)	47	53	40	22.50 (4.30)	100	109.70 (7.90)
McAlonan et al,[39] 2002	17	32.00 (10.00)	NA	96.00 (15.00)	100	0	24	33.00 (7.00)	92	114.00 (14.00)
Rojas et al,[40] 2006	24	20.79 (10.58)	100	94.75 (20.64)	0	100	23	21.41 (10.91)	100	118.74 (11.18)
Schmitz et al,[41] 2006	10	38.00 (9.00)	100	105.00 (14.00)	80	20	12	39.00 (6.00)	100	106.00 (13.00)
Toal et al,[42] 2010	...	...	...	...	...	...	33	32.00 (9.00)	90.91	105.00 (12.00)
Asperger disorder sample	39	32.00 (12.00)	89.74	106.00 (15.00)	100	0	...	...	...	...
Autistic disorder sample	26	30.00 (8.00)	80.77	84.00 (23.00)	0	100	...	...	...	...
Wilson et al,[43] 2009	10	30.10 (9.18)	80	91.50 (19.67)	0	100	10	29.40 (7.91)	70	127.20 (9.00)
Total	**496**	20.07 (10.86)	89	99.65 (21.61)	31	53	471	19.60 (10.55)	88	110.17 (13.42)

Abbreviations: Ellipses, not applicable; NA, data not available.
[a] Missing information for 3 participants.

Table 2. Regions Showing Statistically Significant Differences in Gray Matter Volume Between Participants With ASD and Healthy Control Individuals[a]

Variable	Talairach Coordinates	SDM Value	No. of Voxels	Cluster Breakdown (No. of Voxels)
Gray matter volume decreases				
Right amygdala-hippocampus complex	28, –4, –20	–0.125	112	Right amygdala (77 voxels) Right hippocampus (13 voxels) Right claustrum (13 voxels)
Right medial parietal cortex	24, –46, 56	–0.107	97	Right superior parietal lobule BA7 and BA5 (32 voxels) Right subgyral parietal lobe BA40 and BA7 (26 voxels) Right medial parietal cortex BA7 (19 voxels) Right postcentral gyrus BA5 (14 voxels)
Left medial parietal cortex	–2, –58, 48	–0.106	66	Left medial parietal cortex BA7 (54 voxels) Right medial parietal cortex BA7 (12 voxels)
Left amygdala-hippocampus complex	–24, –22, –22	–0.103	18	Left parahippocampal gyrus BA35 (13 voxels)
Gray matter volume increase				
Left middle frontal gyrus	–36, 38, 12	0.116	15	Left middle frontal gyrus BA10 and BA46 (11 voxels) Left inferior frontal gyrus BA46 (4 voxels)

Abbreviations: ASD, autism spectrum disorder; BA, Brodmann area; SDM, Signed Differential Mapping.
[a] $P < .001$ for all.

The bilateral medial parietal cortex remained significant in all but 1 combination of data sets. The left middle-inferior frontal gyrus was somewhat less robust, failing to reach significance in 4 combinations of studies. The analyses of quartiles showed that at least 25% of the studies had found a decrease of gray matter in the right amygdala-hippocampus complex and the bilateral precuneus but not the other 2 regions.

Because there was a partial sample overlap between 2 sets of studies (Rojas et al[40] with Wilson et al[43] and

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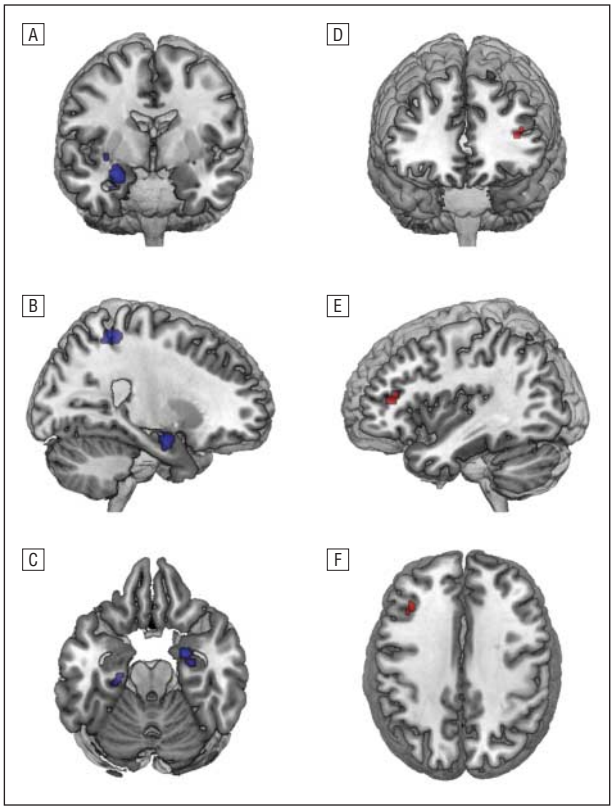

Figure 2. Regions of gray matter volume difference between participants with autism spectrum disorder (ASD) and healthy control individuals. A-C, Gray matter volume reductions in ASD (3-dimensional view). A, Right amygdala (coronal and radiologic view); B, right amygdala, right precuneus (sagittal view); and C, bilateral amygdala-hippocampus complex (transversal and neurologic view). D-F, Gray matter volume increase in the left middle-inferior frontal gyrus in ASD (3-dimensional view). D, Coronal and radiologic view; E, sagittal view; and F, transversal and neurologic view.

McAlonan et al[39] with Toal et al[42]), we next repeated the analyses excluding the studies with the smallest samples.[39,43] The results remained unchanged when we excluded both of these studies.

Finally, we repeated the analyses excluding the 3 studies that did not use a criterion standard diagnostic tool, such as the Autism Diagnostic Interview–Revised.[21,38,45] The exclusion of these 3 studies did not modify the results.

EFFECTS OF ASD SUBTYPE AND AGE ON GLOBAL AND REGIONAL GRAY MATTER VOLUMES

Eleven data sets (in 10 studies)[35-38,40,43,46,49,51,52] reported global gray matter volumes and the proportion of participants with autistic disorder and those with Asperger disorder in their samples. These studies were included in the ANCOVA of global gray matter differences comparing diagnostic and age subgroups (n=303 healthy controls, 211 autistic disorder patients, and 67 Asperger disorder patients). The results revealed no statistically significant differences in global gray matter volumes between autistic disorder and Asperger disorder or between adult and adolescent ASD samples (Q=0.183, df=2, P=.91; autistic disorder vs Asperger disorder: d=0.009, SD=0.29, z=0.03, P=.98; adults vs adolescents: d=–0.010, SD=0.22, z=–0.42, P=.67).

All but 2 studies[47,53] reported the proportion of participants with autistic disorder and those with Asperger disorder within their samples and could be included in the ANCOVA of regional gray matter differences (n=440 healthy controls, 293 patients with autistic disorder, and 169 patients with Asperger disorder). The Q map of regional gray mater differences (effects of diagnosis and age) found a significant difference in the right precuneus (peak [Talairach]: 22, –48, 54, SDM=1, $P<.001$). This was driven by a significantly greater decrease of gray matter volume in adults than in adolescents (peak [Talairach]: 22, –48, 54, SDM=–0.346, $P<.001$) (**Figure 3**). Crucially, no statistically significant differences were found in regional gray matter volumes between the autistic disorder and Asperger disorder groups (smallest $P\geq.001$) (Figure 3). An additional analysis that included only diagnostically pure samples (ie, composed of only participants with autistic disorder or only those with Asperger disorder) resulted in a nonsignificant Q map (smallest $P\geq.001$), indicating no statistically significant effects of diagnosis or age.

COMMENT

To our knowledge, ours is the first meta-analysis of voxel-based gray matter abnormalities in participants with ASD. It complements other existing meta-analyses of studies using hand-tracing methods.[56] The study is timely, given that findings from previous studies have been relatively inconsistent and that only recently have enough studies been accumulated to allow such meta-analysis. We took advantage of recent developments in meta-analytical methods to compare subtypes of ASD—a subject that is relevant to the current *DSM-5* deliberations—and developed a publically available database, which we hope will facilitate replication and further analyses from researchers in the field. The database is readily accessible at http://www.sdmproject.com/database/.

SUMMARY OF THE MAIN FINDINGS

Twenty-four independent data sets comprising formal comparisons between participants with ASD and healthy controls met inclusion criteria. Although no significant differences in global gray matter volumes existed, participants with ASD showed robust reductions of gray matter volume in the amygdala-hippocampus complex (particularly on the right side) and medial parietal regions (precuneus, BA7). A small increase in gray matter volume was found in the left middle and inferior frontal gyri (BA46 and BA10). Overall, these findings were robust because they consistently emerged using multiple statistical approaches and various sensitivity and subgroup analyses. No significant differences in regional gray matter volume were found between participants with a diagnosis of autistic disorder vs Asperger disorder. Decreases of gray matter volume in the right precuneus were sta-

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Table 3. Jackknife Sensitivity and Quartiles Analyses

Source	Decreased Gray Matter Volume: Right Amygdala-Hippocampus Complex	Decreased Gray Matter Volume: Left Amygdala-Parahippocampus Complex	Decreased Gray Matter Volume: Bilateral Medial Parietal Cortex	Increased Gray Matter Volume in Left Middle Frontal Gyrus
Jackknife sensitivity analysis, discarded study				
Abell et al,[21] 1999	Yes	Yes	Yes	Yes
Boddaert et al,[44] 2004	Yes	Yes	Yes	Yes
Bonilha et al,[45] 2008	Yes	Yes	Yes	Yes
Brieber et al,[46] 2007	Yes	No	Yes	Yes
Craig et al,[35] 2007	Yes	Yes	Yes	Yes
Ecker et al,[36] 2009	Yes	No	No	No
Freitag et al,[47] 2008	Yes	Yes	Yes	Yes
Hardan et al,[48] 2003 (Asperger disorder sample)	Yes	Yes	Yes	Yes
Hardan et al,[48] 2003 (Autistic disorder sample)	Yes	Yes	Yes	Yes
Hyde et al,[37] 2009	Yes	Yes	Yes	No
Ke et al,[49] 2008	Yes	Yes	Yes	Yes
Kosaka et al,[38] 2010	Yes	Yes	Yes	Yes
Kwon et al,[50] 2004 (Asperger disorder sample)	Yes	Yes	Yes	Yes
Kwon et al,[50] 2004 (Autistic disorder sample)	Yes	Yes	Yes	Yes
Langen et al,[51] 2009	Yes	Yes	Yes	Yes
McAlonan et al,[39] 2002	Yes	Yes	Yes	Yes
McAlonan et al,[52] 2008 (Asperger disorder sample)	Yes	Yes	Yes	Yes
McAlonan et al,[52] 2008 (Autistic disorder sample)	Yes	Yes	Yes	Yes
Rojas et al,[40] 2006	Yes	Yes	Yes	Yes
Schmitz et al,[41] 2006	Yes	Yes	Yes	No
Toal et al,[42] 2009 (Asperger disorder sample)	Yes	Yes	Yes	Yes
Toal et al,[42] 2009 (Autistic disorder sample)	Yes	Yes	Yes	Yes
Waiter et al,[53] 2004	Yes	Yes	Yes	No
Wilson et al,[43] 2009	Yes	Yes	Yes	Yes
Total (24 data sets)	**24**	**22**	**23**	**20**
Quartiles analysis				
First quartile (25%)	Yes	No	Yes	No
Second quartile (median)	No	No	No	No
Third quartile (75%)	No	No	No	No

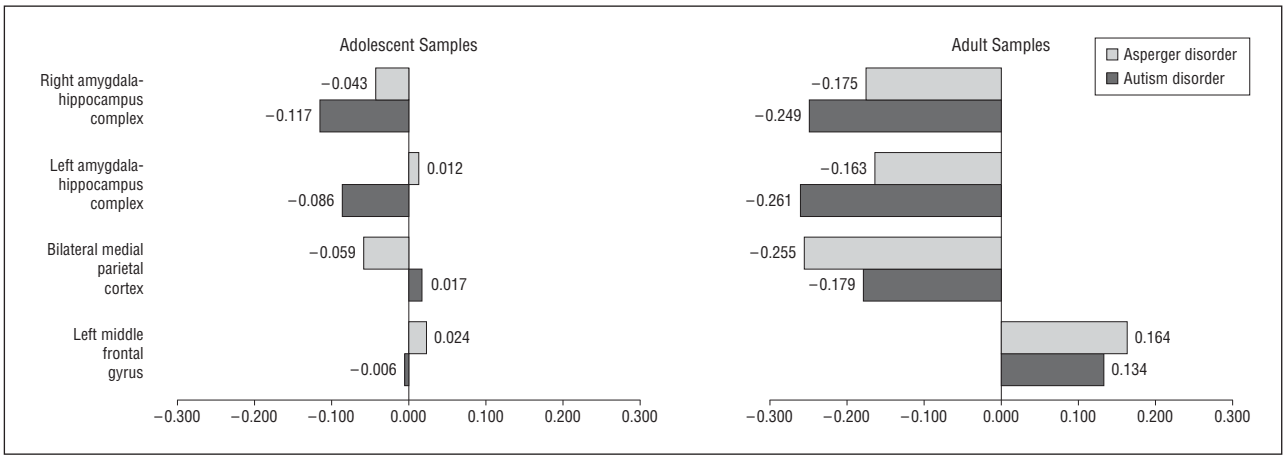

Figure 3. Contribution of diagnostic group and age to the main results. Data shown are Signed Differential Mapping values, ranging from –1 to 1.

tistically higher in adults than in adolescents with ASD. Each of these findings is discussed in turn.

Reduced Gray Matter Volume in Amygdala-Hippocampus Complex

The amygdala-hippocampus complex and adjacent cortical regions (eg, parahippocampal gyrus) have long been hypothesized to be involved in ASD.[57,58] For example, lesions in the amygdala cause impairment in social cognition and alterations in salience coding, including processing of emotional information from faces,[59-64] features that had also been demonstrated to be altered in autism.[65-69]

Structural neuroimaging studies in ASD have reported volumetric abnormalities in the amygdala-hippocampus complex, although the direction of the changes has been

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inconsistent.[11,56] Our results are in agreement with previous reports[70-72] of reduced gray matter volume in this region. Structural abnormalities in the amygdala are consistent with the results of a recent meta-analysis[73] that has shown hypoactivation of this structure in functional neuroimaging tasks related to social proceses.

It is clear that the amygdala and its adjacent structures are implicated in social cognition.[74] Its impairment in ASD is largely supported by tasks involving theory-of-mind processes,[75-80] which require making inferences regarding the mental state of others.[75,81] Although the amygdala is one of the main areas active during these tasks, other brain regions, such as the precuneus and middle-inferior prefrontal areas, also found to be abnormal in this meta-analysis, are implicated too.[78] An alternative, yet not incompatible, interpretation of the findings is that the reported abnormalities in the amygdala-hippocampus may be associated with the extremely high prevalence of emotional disorders in ASD. Indeed, numerous studies[82-84] have shown that participants with ASD have a much higher prevalence of anxiety and mood disorders than would be expected in the general population. The amygdala-hippocampus complex is crucial to the current neurobiological models of anxiety and mood disorders.[85-90] Unfortunately, it is not possible from the current data to establish whether the observed abnormalities predispose individuals to developing anxiety or mood disorders, are the consequence of these comorbidities, or both.

Reduced Gray Matter Volume in Medial Parietal Cortex (Precuneus)

The precuneus is a posteromedial area in the parietal lobe that has been poorly studied in the past because of its broad connections with other brain regions and the rarity of specific lesions in this area. To our knowledge, there are no previous studies in ASD in which the parietal cortex has been selected as an ROI. However, in addition to the VBM studies included in this meta-analysis, at least 2 previous ASD studies[91,92] reported abnormal cortical thickness in this region using surface-based morphometry methods.

A recent functional neuroimaging study[93] provides interesting information regarding the role of the precuneus and its possible role in ASD. Specifically, the precuneus has been implicated in the processing of the self (ie, the representation and awareness of the self, integral to many aspects of social cognition), which has in turn been found to be impaired in autism.[94,95]

Supporting its role in social functions, the precuneus and medial prefrontal areas (including those reported in this meta-analysis) are implicated in the so-called mirror neuron system, which is involved in action-perception linkage and has been hypothesized to underlie empathy and social insight.[96] Dysfunction of the mirror neuron system in ASD (the broken mirror hypothesis) has been suggested and is currently a topic of considerable debate.[97-103]

The precuneus is also involved in visuospatial imagery, and several studies[104] have found unusual connectivity in participants with ASD when performing visuospatial imagery tasks. Different visual abnormalities have been proposed to cause many of the behavioral signs and symptoms of ASD, some of them specifically affecting the development of social cognitive skills.[105] A third function in which the precuneus is implicated is episodic memory, which is known to be specifically impaired in ASD.[106,107]

Increase in Gray Matter in the Left Middle-Inferior Frontal Cortex

It is well known that lesions in prefrontal regions and their connections with other brain areas, such as the precuneus and the amygdala, cause marked impairment in social cognition.[108-112] Frontal brain areas have previously been proposed to be involved in ASD,[76-79] including the middle and inferior frontal gyri, although the precise regions obtained in our study (BA46 and BA10) have been less well studied in ASD. However, our findings in these regions were somewhat less robust because they failed to remain significant in some of the reliability analyses; thus, these findings need to be interpreted with caution.

Absence of Gray Matter Volume Differences Between Autistic Disorder and Asperger Disorder

An ongoing debate exists as to whether autistic disorder and Asperger disorder are 2 separate disorders or represent a single nosologic entity with varying degrees of severity.[113,114] We did not find statistically significant differences in gray matter volume between the autistic disorder and Asperger disorder groups. These findings would suggest that both disorders, as diagnosed in studies to date, have similar neural substrates and support the view of a single nosologic entity with differing degrees of severity. Thus, our results would be consistent with the proposal in the current draft of the *DSM-5* to subsume autistic disorder and Asperger disorder (as well as pervasive developmental disorder not otherwise specified) into a single, broader ASD category.[17] It is, of course, still possible that each of these disorders may prove to be etiologically heterogeneous.

Differences Between Adult and Adolescent ASD Samples

Generally, the findings were more pronounced in adult than adolescent samples, but the only statistically significant difference was a greater gray matter volume reduction in the precuneus in adult compared with adolescent samples. Whether these differences are the result of developmental maturational processes or reflect secondary effects of living with cognitive differences is unclear because little is known about the role of this brain region in ASD. One functional neuroimaging study[115] has recently reported age-related changes in the neural correlates of empathy (including decreases in activation in the right precuneus) in healthy participants.

Age-related changes in ASD may result from dynamic processes in brain structure and function across the lifespan.[116] It is known that children and adoles-

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cents with ASD can show a surprising degree of age-related clinical improvement.[117] It is therefore possible that a selection bias exists, whereby older participants may have a more disabling form of the disorder and thus display more prominent gray matter abnormalities. Unfortunately, few magnetic resonance imaging studies have included young children, and it was difficult to fully explore age-related differences in brain structure in this meta-analysis. Longitudinal studies tracking individuals with a range of outcomes are clearly needed to examine this question.

In any case, these results need to be interpreted cautiously because additional analyses that include only diagnostically pure samples (ie, composed of only participants with autistic disorder or only those with Asperger disorder) revealed no statistically significant age effects. This finding could be indicative of insufficient statistical power to examine age-related effects.

STRENGTHS AND LIMITATIONS

The main strengths of this study are the unbiased inclusion of published and unpublished studies, even if their results were negative (ie, when no significant differences between participants with ASD and controls were found) and the use of novel voxel-wise meta-analytic methods.[27,28] The online database containing all the data and methodologic details from every study included in this meta-analysis will be a useful resource. It is important to highlight several limitations of this study, some of which are inherent to all meta-analytical approaches. First, despite our attempts to include as many unpublished VBM studies as possible, the possibility of publication bias cannot be entirely ruled out. Second, voxel-based meta-analyses are based on summarized (ie, coordinates from published studies) rather than raw data, which may result in less accurate results.[16] However, obtaining the raw images from the original studies is logistically difficult. Third, although our method provides excellent control for false-positive results, it is more difficult to completely avoid false-negative results. Fourth, our comparison of results from groups with autistic disorder vs Asperger disorder may be limited by the method and accuracy of the specific diagnoses in the contributing studies; it can be extremely hard, for example, to obtain reliable developmental history (eg, age of first words and phrases) from parents of adults. Fifth, studies retrieved were generally homogeneous in terms of sex (predominantly male), IQ (mostly high functioning), and age (predominantly adults and adolescents), which may not represent the entire autistic spectrum. For example, in the general population, approximately 60% of all participants with ASD have an IQ below 70.[2] Therefore, the current results may not generalize to female participants, those with an IQ below 70, or younger patients with ASD.

In conclusion, our meta-analysis provides a quantitative summary of VBM studies in ASD and helps resolve some of the relatively inconsistent results in this literature. Abnormalities in bilateral amygdala-hippocampus, precuneus, and left prefrontal areas in ASD are all indicative of a dysfunctional network of social brain regions and consistent with the defining features of this sociocommunicative disorder. In addition, our results suggest common structural abnormalities between high-functioning autistic disorder and Asperger disorder, which support the proposal of a single category of ASD in the *DSM-5*.

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