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ORIGINAL ARTICLE

Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder *versus* healthy controls

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Background. We conducted a meta-analysis of voxel-based morphometry (VBM) studies in autism spectrum disorder (ASD) to clarify the changes in regional white-matter volume underpinning this condition, and generated an online database to facilitate replication and further analyses by other researchers.

Method. PubMed, ScienceDirect, Web of Knowledge and Scopus databases were searched between 2002 (the date of the first white-matter VBM study in ASD) and 2010. Manual searches were also conducted. Authors were contacted to obtain additional data. Coordinates were extracted from clusters of significant white-matter difference between patients and controls. A new template for white matter was created for the signed differential mapping (SDM) meta-analytic method. A diffusion tensor imaging (DTI)-derived atlas was used to optimally localize the changes in white-matter volume.

Results. Thirteen datasets comprising 246 patients with ASD and 237 healthy controls met inclusion criteria. No between-group differences were found in global white-matter volumes. ASD patients showed increases of white-matter volume in the right arcuate fasciculus and also in the left inferior fronto-occipital and uncinate fasciculi. These findings remained unchanged in quartile and jackknife sensitivity analyses and also in subgroup analyses (pediatric *versus* adult samples).

Conclusions. Patients with ASD display increases of white-matter volume in tracts known to be important for language and social cognition. Whether the results apply to individuals with lower IQ or younger age and whether there are meaningful neurobiological differences between the subtypes of ASD remain to be investigated.

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Introduction

Autistic spectrum disorders (ASD), including autism and Asperger's syndrome, are characterized by impairments in social interaction, communication and imagination, in addition to a rigid, repetitive pattern of behavior (Wing, 1996; APA, 2000). The prevalence of ASD is estimated to be approximately 9/1000 children and is more frequent in males [Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators; Centers for Disease Control and Prevention (CDC), 2009]. In adults, the prevalence of ASD might be similar (Brugha *et al*. 2009).

The precise etiology of ASD is unknown but it is thought to have a strong genetic basis (Volkmar *et al*. 1998; Abrahams & Geschwind, 2008). There is a large body of evidence highlighting the role of abnormal brain development in ASD (Schultz, 2005). For example, structural neuroimaging studies have identified several brain systems implicated in the disorder, including the cerebellum, visual cortex, amygdala and hippocampus (Abell *et al*. 1999; McAlonan *et al*. 2002, 2008; Waiter *et al*. 2004; Brieber *et al*. 2007; Craig *et al*. 2007; Bonilha *et al*. 2008; Ke *et al*. 2008; Toal *et al*. 2009). Functional neuroimaging studies have reported reduced activations in the amygdala and related limbic regions, including the cingulate cortex (Baron-Cohen *et al*. 1999; Pierce *et al*. 2001; Ashwin *et al*. 2007), all of

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which are thought to be consistent with the deficits in social behavior that are characteristic of the disorder (Baron-Cohen *et al*. 2000).

A complementary and potentially more informative approach would be to identify systems-level or 'supraregional' brain abnormalities in ASD rather than within discrete brain regions. Cortical and subcortical regions that are altered in ASD are interconnected through a complex system of short- and long-range tracts running within the white matter of each hemisphere. Regional white-matter abnormalities in ASD have been investigated using different methods, including a region of interest (ROI) approach on structural magnetic resonance imaging (MRI) scans (e.g. T2-weighted images) and more recent tract-specific dissections of diffusion tensor imaging (DTI) datasets. These approaches are mainly hypothesis driven and therefore have been usually limited to single structures such as the corpus callosum (Piven *et al*. 1997; Hardan *et al*. 2000), cerebellar tracts (Catani *et al*. 2008) and the cingulum (Pugliese *et al*. 2009). This paucity of research might be due partially to the difficulties of manually delimiting some white-matter regions, which is time-consuming and requires extensive anatomical knowledge (Waiter *et al*. 2005).

The recent development of fully automated, whole-brain, voxel-based morphometry (VBM) methods (Ashburner & Friston, 2000, 2001; Mechelli *et al*. 2005), which overcome the difficulties in the manual delimitation of white-matter regions, provides a powerful tool to study the potential changes in white-matter volume in ASD. Unfortunately, recent applications of these novel methods to the study of white-matter volumetric changes in ASD are often limited by relatively small sample sizes, resulting in insufficient statistical power. In this context, we considered it timely to perform a voxel-based quantitative meta-analysis of all published VBM studies in ASD reporting changes in white-matter volume. For this purpose, we have adapted an existing meta-analytical method, signed differential mapping (SDM) (Radua & Mataix-Cols, 2009; Radua *et al*. 2010), for its application to white-matter studies. To facilitate replication and further analyses by other colleagues, we have also developed a readily accessible online database (www.sdmproject.com/database), which contains all the data and methodological details from every study included in this meta-analysis.

Method

Criteria for inclusion and exclusion of studies

We conducted a comprehensive literature search of studies conducting T1- or T2-weighted VBM comparisons between patients with ASD and healthy controls published between 2002 (the date of the first white-matter VBM study in ASD) and September 2010 using the PubMed, ScienceDirect, Web of Knowledge and Scopus databases. The search keywords were 'Asperger' or 'autism', plus 'morphometry', 'voxel-based' or 'voxelwise'. In addition, we conducted manual searches within several review papers and the reference sections of the articles obtained. Studies containing duplicated datasets (i.e. analyzed the same data in different manuscripts) and studies with less than 10 patients were excluded. Next, the corresponding authors were contacted by email requesting any details not included in the original manuscripts. MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (Stroup *et al*. 2000) were followed in the study.

Comparison of global and regional white-matter volumes

Meta-analytical differences in global white-matter volumes were calculated using standard random-effects models with the 'globals' procedure in SDM software (www.sdmproject.com/), which uses restricted maximum-likelihood estimation of the variance, a fitting method that has been recommended for its good balance between unbiasedness and efficiency (Viechtbauer, 2005).

Regional differences in white-matter volume between patients and controls were also analyzed using SDM, a novel voxel-based meta-analytic approach that improves upon other existing methods (Turkeltaub *et al*. 2002; Wager *et al*. 2007) and has been used in previous meta-analyses of VBM studies (Radua & Mataix-Cols, 2009; Bora *et al*. 2010; Radua *et al*. 2010). The main advantage of SDM is that it uses the reported peak coordinates to recreate maps of the signed (i.e. positive and negative) volume differences between patients and controls, rather than just assessing the probability or likelihood of a peak. This unique feature makes SDM an optimal method for comparing patients with controls without biasing the results towards those brain regions with more inter-study heterogeneity (Radua & Mataix-Cols, 2010). The SDM methods have been reported in detail elsewhere (Radua & Mataix-Cols, 2009) and are only described briefly here. First, peak coordinates of white-matter differences between patients and controls are extracted from each dataset. Importantly, those peaks that are not statistically significant at the whole-brain level are excluded. That is, although different studies may use different thresholds, we ensure that the same statistical threshold throughout the brain is used within each study. This is intended to avoid biases

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towards liberally thresholded brain regions, as 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 standard Talairach map of the differences in white matter is recreated separately for each study by means of a Gaussian kernel that assigns higher values to the voxels closer to peaks. This includes limiting voxel values to a maximum to avoid biases towards studies reporting various coordinates in close proximity, and reconstructing both increases and decreases of white-matter volume in the same map. Third, the mean map is obtained by calculating voxelwise 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 more. This analysis is complemented with additional analyses to assess the robustness of the findings (Radua & Mataix-Cols, 2009), namely descriptive analyses of quartiles to find the actual proportion of studies reporting results in a particular brain region (regardless of *p* values) and jackknife sensitivity analyses to assess the reproducibility of the results. Statistical significance is determined using standard randomization tests, thus creating null distributions from which *p* values can be obtained directly (Radua & Mataix-Cols, 2009). The reproducibility of the results was also assessed by analyzing pediatric and adult samples separately, although we could not perform formal statistical tests given the small number of studies in each group.

In this study, we adapted SDM for its use in white-matter VBM studies. It should be noted that the null hypothesis of the standard randomization test is that peak coordinates are distributed uniformly throughout all the gray matter of the brain. The test consists in randomly relocating the original peak coordinates in all gray-matter voxels as defined by a gray-matter randomization template, and comparing the original values with the values obtained from these randomizations (Wager *et al*. 2007). However, we aimed to assess the statistical significance of white- (rather than gray-) matter volumes, and thus we needed to create a specific white-matter randomization template. Otherwise, the use of a gray-matter randomization template to assess white-matter volumes would be equivalent to the use of the body weight variance to assess the statistical significance of body height differences. The white-matter mask was created with the standard parameters for gray-matter masks (Wager *et al*. 2007), but including white instead of gray matter. This new mask is included in a new, readily available version of SDM software (www.sdmproject.com/) to allow other researchers to conduct statistically correct voxel-based meta-analyses of white-matter studies. No other aspects of the original method were modified.

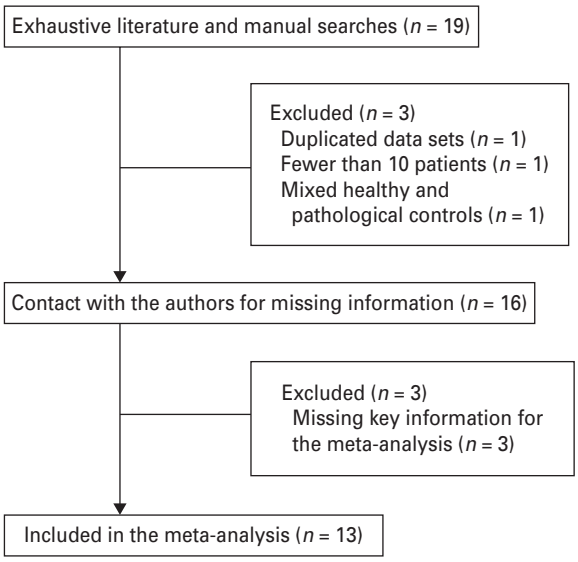

Fig. 1. Inclusion of studies.

Localization of changes in white-matter volume

A DTI-derived atlas (Catani & Thiebaut de Schotten, 2011) was used to optimally localize the changes in white-matter volume detected in our meta-analysis. This atlas provides digital maps of long-range white-matter tracts normalized in a common space of reference. The maps are derived from virtual *in vivo* dissections (Catani *et al*. 2002; Catani & Thiebaut de Schotten, 2008) of diffusion tensor datasets and provide information on the degree of anatomical variability within the normal population by quantifying the percentage of overlap for each single voxel (e.g. 50, 75 and >90%). The results from the VBM meta-analyses were therefore overlapped on the digital masks of each tract provided in the atlas to localize the regional differences.

Results

Included studies and sample characteristics

As shown in Fig. 1, the search retrieved a total of 17 publications or abstracts comprising 19 studies (that is, independent comparisons between ASD and healthy control samples). Three publications were discarded because they contained duplicated datasets (McAlonan *et al*. 2005), less than 10 patients (Yamasue *et al*. 2005) or a mixed control group that included healthy controls, children with reading disability and children with benign macrocephaly (Bigler *et al*. 2010). After contacting the authors, no methodological ambiguities remained regarding the design or analysis of 11 publications comprising 13 independent comparisons, but three studies had to be excluded because they were

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missing key information for our meta-analysis (i.e. peak coordinates from whole-brain analyses) (Schmitz *et al*. 2007; Hong *et al*. 2008; Langen *et al*. 2009). Therefore, 13 high-quality datasets could be included in this meta-analysis, of which six consisted of adult ASD samples and seven of pediatric or adolescent samples. There was a partial sample overlap between two studies (McAlonan *et al*. 2002; Toal *et al*. 2009). For this reason we conducted the meta-analysis with all studies and then repeated the analyses excluding the latter study. Finally, we were not able to discard a potential overlap in the samples of two other studies (Ke *et al*. 2008, 2009), and therefore we also repeated the meta-analysis excluding the latter.

Combined, the studies included 246 patients with ASD (125 autism; 84 Asperger; 37 unknown) and 237 healthy controls. Patients comprised 133 adults (45 autism; 66 Asperger; 22 unknown) and 113 children/adolescents (80 autism; 18 Asperger; 15 unknown). As shown in Table 1, no relevant differences between patients and controls were found in terms of age and gender, as the original studies were already well matched in this respect. Full IQ was slightly lower in the ASD group, although this difference was largely due to a single study in which the patients had a fairly low IQ (Boddaert *et al*. 2004). Therefore, we also repeated the meta-analysis excluding this study to remove the potential confounding effects of IQ. Further details of each of the included studies, such as co-morbid conditions, medication status or diagnostic criteria, can be found at www.sdmproject.com/database.

Global differences in white-matter volume

Global white-matter volumes were available from five independent datasets within four publications (Waiter *et al*. 2005; Hyde *et al*. 2009; McAlonan *et al*. 2009; Ecker *et al*. 2010). No statistically significant differences in global white-matter volume were found between ASD patients ($n=87$) and healthy controls ($n=108$) [unbiased Hedges' (Hedges & Olkin, 1985) $d=-0.10$, $z=-0.70$, $p=0.481$]. This was true for both pediatric/adolescent (Waiter *et al*. 2005; McAlonan *et al*. 2009) ($d=-0.12$, $z=-0.67$, $p=0.501$) and adult (Hyde *et al*. 2009; Ecker *et al*. 2010) ($d=-0.05$, $z=-0.18$, $p=0.857$) samples. No significant heterogeneity was found in any of the analyses (all studies: $Q=2.16$, 4 df, $p=0.707$; children/adolescents: $Q=0.77$, 2 df, $p=0.680$; adults: $Q=1.35$, 1 df, $p=0.245$).

Regional differences in white-matter volume

Data for this analysis were obtained from all the studies included in the meta-analysis. As shown in Table 2 and Fig. 2, ASD patients showed a large increase in white-matter volume [1187 voxels, maximum at (34, −2, 32), SDM = 0.160] in the right centrum semiovale, comprising the arcuate fasciculus and also a small part of the extreme capsule. Patients also showed a moderately large increase in white-matter volume [418 voxels, maximum at (−26, 6, −4), SDM = 0.159] in the left external/extreme capsule, comprising the inferior fronto-occipital and the uncinate fasciculi. These increases in white-matter volume were detected separately in both pediatric and adult samples [right increase maxima: (38, −4, 40), SDM = 0.122 in children and (30, −6, 22), SDM = 0.337 in adults; left increase maxima: (−28, 4, −2), SDM = 0.159 in children and (−32, −14, −6), SDM = 0.215 in adults], although we could not perform formal statistical tests because of insufficient numbers of pediatric and adult studies. Finally, a small decrease in white-matter volume (15 voxels) in the right anterior cingulum and the corpus callosum was also detected.

The results remained largely unchanged in the analysis of quartiles, with the specified white-matter increases detected in the third quartile map (i.e. at least 25% of the studies had found some increase in those regions) and the anterior cingulum/corpus callosum decrease in the median map. Whole-brain jackknife sensitivity analysis showed that the results were highly replicable, as white-matter increases in the right arcuate fasciculus and in the left inferior fronto-occipital/uncinate fasciculi were preserved in all but one of the combinations of studies. Conversely, a white-matter decrease in the anterior cingulum/corpus callosum failed to emerge in four combinations of studies. Finally, findings were nearly identical when the studies that had a potential sample overlap (Ke *et al*. 2009; Toal *et al*. 2009) or included patients with very low IQ (Boddaert *et al*. 2004) were excluded from the analyses, with the exception of the white-matter volume decrease in the anterior cingulum/corpus callosum, which was no longer significant after the exclusion of Ke *et al*. (2009) and Toal *et al*. (2009).

Discussion

To our knowledge, this is the first meta-analysis of VBM studies of white-matter volume in ASD. The study is timely given that a sufficient number of high-quality studies have only recently become available. The main findings were that individuals with ASD consistently display increases in white-matter volume in the right arcuate fasciculus and left inferior fronto-occipital and uncinate fasciculi. These results were obtained in both pediatric/adolescent and adult samples.

The arcuate fasciculus is a white-matter bundle connecting perisylvian areas in the frontal, parietal

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Table 1. *Demographic and clinical characteristics of the 13 voxel-based morphometry datasets included in the meta-analysis*

	Methodological aspects		Patients						Controls			
	Software (name)	Threshold	*n*	Age ± S.D. (years)	Males (%)	Full IQ ± S.D.	Autism (%)	Asperger (%)	*n*	Age ± S.D. (years)	Males (%)	Full IQ ± S.D.
Boddaert *et al*. (2004)	SPM99	$p<0.05$ corrected	21	9.3 ± 02.2	76	42 ± 21	100	0	12	10.8 ± 02.7	58	N.A.
Bonilha *et al*. (2008)	SPM5	$p<0.05$ corrected	12	12.4 ± 04.0	100	N.A.	100	0	16	13.2 ± 05.0	100	N.A.
Craig *et al*. (2007)	SPM2 + XBAMM	<1 false-positive cluster	14	37.9 ± 11.4	0	103 ± 17	29	71	19	35.0 ± 14.0	0	111 ± 14
Ecker *et al*. (2010)	SPM5	$p<0.001$ uncorrected	22	27.0 ± 07.0	100	104 ± 15	N.A.	N.A.	22	28.0 ± 07.0	100	111 ± 10
Hyde *et al*. (2009)	CIVET	$p<0.05$ corrected	15	22.7 ± 06.4	100	100 ± 13	100	0	15	19.2 ± 05.0	100	107 ± 12
Ke *et al*. (2008)	SPM5	$p<0.001$ uncorrected	17	8.9 ± 02.0	82	109 ± 19	100	0	15	9.7 ± 01.7	80	110 ± 19
Ke *et al*. (2009)	SPM5	$p<0.001$ uncorrected	12	8.8 ± 02.3	100	101 ± 19	100	0	10	9.4 ± 02.1	100	100 ± 18
McAlonan *et al*. (2002)	XBAMM	<1 false-positive cluster	17	32.0 ± 10.0	N.A.	96 ± 15	0	100	24	33.0 ± 07.0	92	114 ± 14
McAlonan *et al*. (2009)												
Asperger sample	XBAMM	<1 false-positive cluster	18	11.2 ± 02.5	83	N.A.	0	100	55	10.7 ± 02.7	85	N.A.
Autism sample	XBAMM	<1 false-positive cluster	18	11.6 ± 03.0	83	N.A.	100	0				
Toal *et al*. (2009)												
Asperger sample	SPM2 + XBAMM	<1 false-positive cluster	39	32.0 ± 12.0	90	106 ± 15	0	100	33	32.0 ± 09.0	91	105 ± 12
Autism sample	SPM2 + XBAMM	<1 false-positive cluster	26	30.0 ± 08.0	81	84 ± 23	100	0				
Waiter *et al*. (2005)	SPM2	$p<0.05$ corrected	15	15.2 ± 02.2	100	100 ± 22	N.A.	N.A.	16	15.5 ± 01.6	100	100 ± 18
Total			246	21.4 ± 12.5	84[a]	94 ± 25[a]	60[a]	40[a]	237	20.4 ± 11.9	83	108 ± 14[a]

CIVET, An image processing environment; IQ, intelligence quotient; N.A., not available; S.D., standard deviation; SPM, statistical parametric mapping; XBAMM, brain activation and morphological mapping.

[a] Result obtained after imputation of missing values using the mean.

Table 2. *Regional differences in white matter volume between individuals with autistic spectrum disorders and healthy controls*

	Maximum			Cluster		Jackknife sensitivity analysis (combinations of studies detecting the difference)
	Talairach coordinates	SDM value	Uncorrected *p*	No. of voxels	DTI atlas-derived main tracts	
Increase of white-matter volume (ASD > healthy)						
R centrum semiovale	34, −2, 32	0.160	0.00001	1187	R arcuate fasciculus R extreme capsule	12 out of 13
L external/extreme capsule	−26, 6, −4	0.159	0.00001	418	L uncinate fasciculus L inferior fronto-occipital fasciculus	12 out of 13
Decrease of white-matter volume (ASD < healthy)						
R anterior cingulum	−4, 24, 20	−0.254	0.0006	15	R anterior cingulum/corpus callosum	9 out of 13

DTI, Diffusion tensor imaging; L, left; R, right; SDM, signed differential mapping.

and temporal lobes (Fig. 2, top left). In the left hemisphere, it connects the classical brain language regions: Wernicke's territory in the superior temporal gyrus, Broca's territory in the inferior frontal gyrus, and the recently confirmed Geschwind's territory in the inferior parietal lobule (Catani *et al*. 2005; Makris *et al*. 2005). In the right hemisphere it participates in visuospatial processing and other aspects of language, including affective prosody and semantics (Heilman *et al*. 1975; Ross & Monnot, 2008). Lesions to the right arcuate fasciculus impair understanding and production of modulation of pitch, intonation contours, melody, cadence, loudness, tempo, stress, accent and pauses (Tucker *et al*. 1977; Bowers *et al*. 1987). Prosody is used to transmit information above and beyond verbal-linguistic intent and to clarify the meaning of potentially ambiguous sentences by the judicious use of pauses and stresses (Ross, 2010). Our findings of increased white matter in this region could represent the anatomical correlate of some of the verbal and nonverbal communication impairments observed in ASD (Koning & Magill-Evans, 2001; Shriberg *et al*. 2001). Recent DTI studies in patients with ASD have found abnormal diffusivities in the arcuate fasciculus, suggesting that changes in volume detected by VBM studies could be accompanied by microstructural abnormalities of the axonal membranes and/or myelin (Kumar *et al*. 2009; Fletcher *et al*. 2010; Knaus *et al*. 2010).

The uncinate fasciculus (Fig. 2, bottom left) is a hook-shaped bundle that connects the inferior frontal gyrus and the inferior surfaces of the frontal lobe with the anterior portions of the temporal lobe, including the cortical nuclei of the amygdala (Ebeling & von Cramon, 1992; Hasan *et al*. 2009). It has traditionally been considered to be part of the limbic system and is known for its involvement in human emotion processing, memory and language functions (Schmahmann *et al*. 2007), all of which are impaired in ASD. Our findings of increased white matter in this regions are thus consistent with a substantial body of evidence from both structural (Stanfield *et al*. 2008) and functional (Baron-Cohen *et al*. 1999; Monk *et al*. 2010) neuroimaging studies implicating the amygdala and related limbic structures in ASD. Several DTI studies in patients with ASD have also found abnormalities in this fasciculus (Kumar *et al*. 2009; Pugliese *et al*. 2009). These abnormal limbic circuits may be related to some of the social and communication impairments typically found in people with ASD (Damasio & Maurer, 1978; Courchesne & Pierce, 2005; Wickelgren, 2005). A recent DTI tractography study found abnormalities in the uncinate fasciculus of adults with psychopathy (Craig *et al*. 2009). These anatomical changes correlated with the severity of antisocial behavior, suggesting that uncinate abnormalities may underpin the neurobiological basis of social impairment irrespective of the etiology. Finally, changes in this uncinate connections may also account for the much higher prevalence of emotional disorders than would be expected in the general population, particularly anxiety and mood disorders in ASD (Ghaziuddin & Greden, 1998; Ghaziuddin *et al*. 1998; Gadow *et al*. 2005). Less is known about the inferior fronto-occipital fasciculus (Fig. 2, top right), although it has been suggested that it may also be involved in language as its electrical

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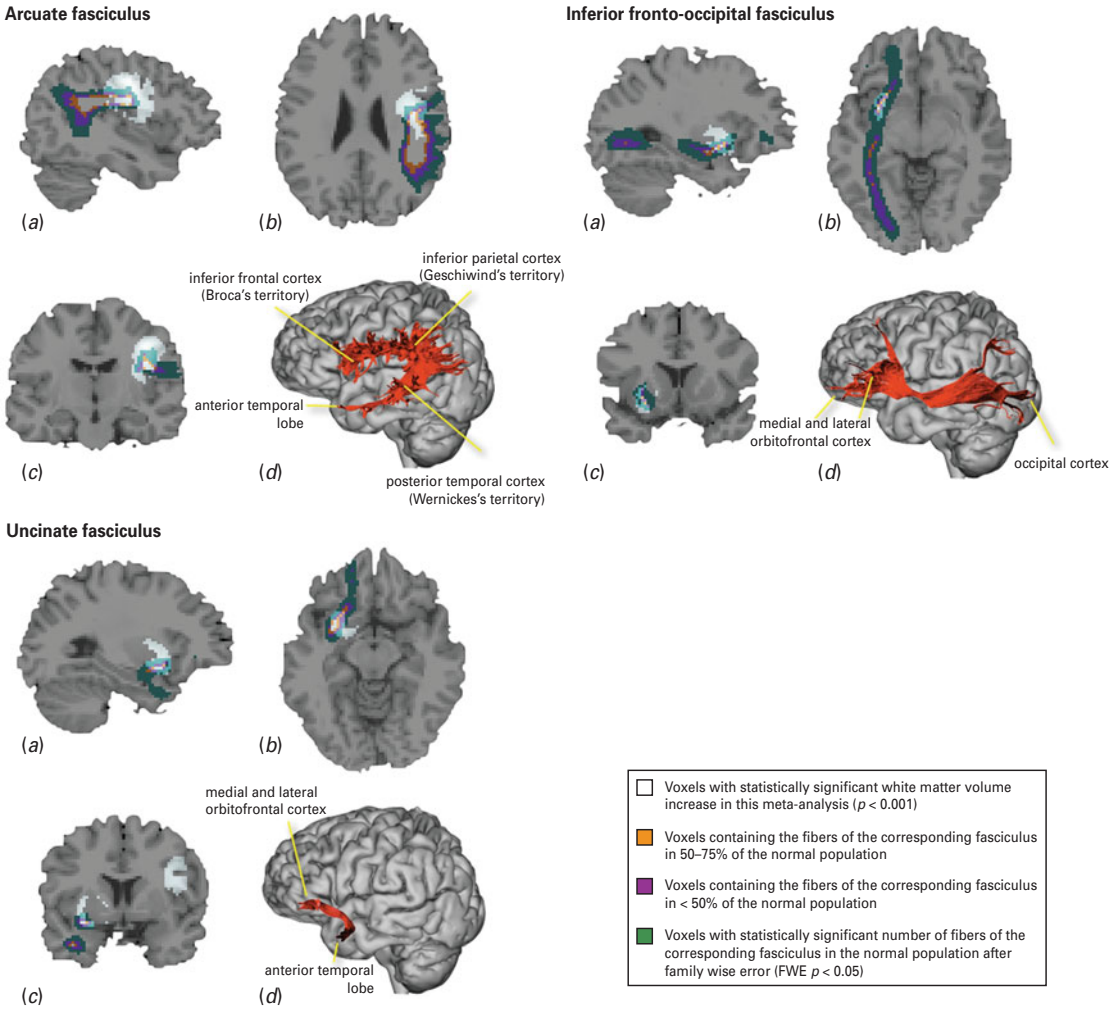

Fig. 2. Main increased white-matter regions in individuals with autistic spectrum disorders (ASD) compared with healthy controls. Localization of the white-matter changes in the right arcuate fasciculus (top left), the left inferior fronto-occipital fasciculus (top right) and the left uncinate fasciculus (bottom left). (*a–c*) Overlapping between the white-matter maps of the meta-analysis (white area) and the digital maps of the corresponding fasciculus derived from an atlas of human brain connections (Catani & Thiebaut de Schotten, 2011). The different colors indicate the percentage of overlap of the voxel containing the fibers of the fasciculus in the normal population. The green voxels represent voxels that are visited by a statistically significant number of fibers of the fasciculus in the normal population after family-wise error (FWE) correction. (*d*) Tractography reconstruction of the fasciculus, modified from Catani *et al*. (2002).

stimulation induces semantic paraphasias (i.e. errors with regard to the meaning of the word target) (Duffau *et al*. 2005).

A small decrease of white matter in the anterior cingulum/corpus callosum was also detected, although the jackknife sensitivity analysis suggested that this may be a less robust finding. Nevertheless, this finding echoes some other studies reporting decreased volume of the anterior cingulum and corpus callosum using manual delimitation methods (Haznedar *et al*. 1997; Cody *et al*. 2002; Stanfield *et al*. 2008) and also DTI methods (Alexander *et al*. 2007; Kumar *et al*. 2009). The adjacent cingulate cortex has a well-documented role in social cognition (Hadland *et al*. 2003; Shinozaki *et al*. 2007) and has been found to be hypoactivated in patients with ASD while performing social tasks (Di Martino *et al*. 2009).

It is important to emphasize that all but one of the studies included in this meta-analysis recruited patients who, on average, had normal IQ. The exclusion of the only study that recruited individuals with mental retardation (Boddaert *et al*. 2004) from the meta-analysis did not modify the results. Therefore, it is fair to conclude that our results may only apply to individuals with 'high functioning' ASD. Whether patients with lower IQs will display

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a different set of volumetric changes remains to be investigated.

Strengths and limitations

A major strength of the study is the development of a new white-matter-specific template for SDM. This template was needed to randomly relocate the white-matter peak coordinates in a white-matter template, as using a gray-matter randomization template to assess differences in white-matter volumes would be statistically incorrect. We hope that the creation of a publicly available database with all the data and methodological details from every study included in this meta-analysis (www.sdmproject.com/database) will facilitate future reviews and meta-analyses as the body of evidence continues to grow.

There are also several limitations, some of which are inherent to all meta-analytical approaches. First, voxel-based meta-analyses are based on summarized (i.e. coordinates from published studies) rather than raw data and this may result in less accurate results (Salimi-Khorshidi *et al*. 2009). However, obtaining the raw images from the original studies is logistically difficult. Second, the different studies included in this meta-analysis used different statistical thresholds. However, it should be noted that, although thresholds involving correction for multiple comparisons are usually preferred, the inclusion of studies with more liberal thresholds is still statistically correct. Indeed, SDM preprocessing uses the coordinates of the voxels with highest differences to approximately recreate the statistical parametric map, but does not make assumptions about whether these differences were significant or not. Third, although voxelwise meta-analytical methods provide excellent control for false-positive results, it is more difficult to completely avoid false-negative results (Salimi-Khorshidi *et al*. 2009). Fourth, there are some inherent limitations to the VBM method, such as reduced effectiveness to detect spatially complex and subtle group differences (Davatzikos, 2004). Fifth, some of the included studies reported white-matter density rather than volume. It should be noted that white-matter density might be understood as a type of white-matter volume that has not been corrected by the distorting effects of the normalization to the stereotactic space; therefore, its inclusion in the meta-analysis is valid (it is also a 'volume') although it may add a source of noise. Sixth, there were too few studies to conduct separate subanalyses in children/adolescents and adults with ASD, although our descriptive analyses suggested that the results were similar in these two age groups. Because the mean age of the 'pediatric' subgroup was 11.0 ± 3.3 years, one remaining question is whether younger patients with ASD may show a distinctive pattern of volumetric changes. Indeed, global brain volume increases in ASD have been mainly reported in childhood autism and are thought to be related to an early acceleration in brain growth (Courchesne *et al*. 2001; Aylward *et al*. 2002; Carper *et al*. 2002; Hazlett *et al*. 2005) but might not persist into adulthood (Aylward *et al*. 2002). Finally, a formal comparison between the two main subtypes of ASD (i.e. autism and Asperger's syndrome) was not possible because of the insufficient number of studies. This might be important because some studies have suggested that there may be some differences in brain structure and function between these subtypes (Ghaziuddin *et al*. 1995; Ghaziuddin & Mountain-Kimchi, 2004; Kwon *et al*. 2004), although this evidence is still preliminary and the distinction remains a matter of debate (Howlin, 2003; Klin *et al*. 2005; Volkmar *et al*. 2009). Even less is known about the neural substrates of the miscellaneous pervasive developmental disorder not otherwise specified (PDD NOS) category, despite being by far the most prevalent (Volkmar *et al*. 2009).

Conclusions

Taken together, the results from this meta-analysis suggest that patients with ASD display increases in white-matter volume in specific white-matter tracts, known to be important for language and social cognition. Whether the results apply to individuals with lower IQ or younger age and whether there are meaningful neurobiological differences between the subtypes of ASD remain to be investigated. Similarly, direct comparisons with other neurodevelopmental disorders are needed to establish the specificity of the findings.

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Declaration of Interest

None.

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