◆ Human Brain Mapping 33:1470–1489 (2012) ◆

Brain Structure Anomalies in Autism Spectrum Disorder—A Meta-Analysis of VBM Studies Using Anatomic Likelihood Estimation

Thomas Nickl-Jockschat,[1,2,3]* Ute Habel,[1,3] Tanja Maria Michel,[1] Janessa Manning,[4] Angela R. Laird,[4] Peter T. Fox,[4] Frank Schneider,[1,3] and Simon B. Eickhoff[1,3,5]

[1]*Department of Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany*
[2]*Institute of Neuroscience and Medicine-1, Forschungszentrum Jülich GmbH, Juelich, Germany*
[3]*JARA – Translational Brain Medicine, Aachen/Juelich, Germany*
[4]*Research Imaging Institute, University of Texas Health Science Center, San Antonio, Texas*
[5]*Institute of Neuroscience and Medicine-2, Forschungszentrum Jülich GmbH, Juelich, Germany*

Abstract: Autism spectrum disorders (ASD) are pervasive developmental disorders with characteristic core symptoms such as impairments in social interaction, deviance in communication, repetitive and stereotyped behavior, and impaired motor skills. Anomalies of brain structure have repeatedly been hypothesized to play a major role in the etiopathogenesis of the disorder. Our objective was to perform unbiased meta-analysis on brain structure changes as reported in the current ASD literature. We thus conducted a comprehensive search for morphometric studies by Pubmed query and literature review. We used a revised version of the activation likelihood estimation (ALE) approach for coordinate-based meta-analysis of neuroimaging results. Probabilistic cytoarchitectonic maps were applied to compare the localization of the obtained significant effects to histological areas. Each of the significant ALE clusters was analyzed separately for age effects on gray and white matter density changes. We found six significant clusters of convergence indicating disturbances in the brain structure of ASD patients, including the lateral occipital lobe, the pericentral region, the medial temporal lobe, the basal ganglia, and proximate to the right parietal operculum. Our study provides the first quantitative summary of brain structure changes reported in literature on autism spectrum disorders. In contrast to the rather small sample sizes of the original studies, our meta-analysis encompasses data of 277 ASD patients and 303 healthy controls. This unbiased summary provided evidence for consistent structural abnormalities in spite of heterogeneous diagnostic criteria and voxel-based morphometry (VBM) methodology, but also hinted at a dependency of VBM findings on the age of the patients. *Hum Brain Mapp 33:1470–1489, 2012.*

Key words: autism spectrum disorder; meta-analysis; brain structure; anatomic-likelihood estimation; cytoarchitectural probabilistic mapping

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: Human Brain Project; Contract grant number: R01-MH074457-01A1; Contract grant sponsor: International Research Training Group; Contract grant number: 1328; Contract grant sponsors: "Rotationsstipendium" RWTH Aachen University; Helmholtz Alliance on Systems Biology; Deutsche Forschungsgemeinschaft.

*Correspondence to: Thomas Nickl-Jockschat, MD, Department of Psychiatry and Psychotherapy, RWTH Aachen University, Pauwelsstrasse 30, D-52074 Aachen, Germany. E-mail: tnickl-jockschat@ukaachen.de

Received for publication 12 April 2010; Revised 10 February 2011; Accepted 11 February 2011

DOI: 10.1002/hbm.21299

Published online 20 June 2011 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Autism spectrum disorders (ASD) are pervasive developmental disorders characterized by a triad of core symptoms: (1) severe and sustained impairment in social interaction, (2) reduced and impaired communication, (3) restricted and/or stereotyped patterns of behavior and interest. Moreover, impairments of sensorimotor functions are regularly present in ASD patients. Disease onset is generally prior to the age of 3 [Volkmar and Pauls, 2003], but clinical presentation of the disorder is complex and can vary considerably. Consequently, the term autism spectrum disorder has been coined to acknowledge the phenotypic variability. The course of the disorder can be further complicated by a variety of diverse comorbidities such as epilepsy [Volkmar and Nelson, 1990], social anxiety disorder, insomnia [Richdale and Prior, 1995], and others.

The exact etiopathological mechanisms of ASD are still ill understood, but compelling evidence supports the idea of ASD as a highly genetically determined neuropsychiatric disorder [Coon, 2006; Courchesne et al., 2007; Landa, 2008; Landa et al., 2007; Lauritsen et al., 2005]. A variety of data points to disturbances of brain growth and maturation as an important pathomechanism. Prospective studies have shown normal brain sizes of ASD patients at birth, but at 1–2 years of age brains of ASD patients undergo abnormal overgrowth [Bartholomeusz et al., 2002; Courchesne et al., 2003; Dawson et al., 2007; Dementieva et al., 2005; Dissanayake et al., 2006; Hazlett et al., 2005]. During later childhood and adolescence, the difference between brain volumes in ASD patients and healthy controls narrows to a remaining of 1–3% difference in brain volume [Redcay and Courchesne, 2005].

Structural MR imaging studies suggest that these altered growth trajectories do not affect the brain ubiquitously. Rather, region of interest (ROI)-based volumetric studies have reported a preferential overgrowth of the frontal and the temporal lobes in particular as well as the amygdala in 2- to 4-year-old ASD patients [Carper and Courchesne, 2005; Carper et al., 2002; Courchesne et al., 2001; Sparks et al., 2002]. In contrast, the occipital lobe is least affected though competing evidence exists [Bloss and Courchesne, 2007; Carper et al., 2002; Hazlett et al., 2005; Kates et al., 2004; Palmen et al., 2005]. In contrast to these findings in children, most volumetric studies on adolescent and adult ASD patients report cortical thinning [Hadjikhani et al., 2006] and normal or even reduced volume of the frontal lobe [Schmitz et al., 2007] and the amygdala [Nacewicz et al., 2006; Pierce et al., 2004; Schumann et al., 2004]. However, volumetric findings in these age groups are inhomogeneous and even contradictory. While some authors did not find abnormally cortical volume reduction [Hardan et al., 2006], others even described a persistence of cortical gray matter enlargement [Lotspeich et al., 2004].

Compared to the depicted volumetric approach, morphometric studies based on voxel-wise whole-brain analyses do not require an *a priori* hypothesis and are hence more sensitive to localized structural changes. Nevertheless, like volumetric investigations, these types of studies also carry several limitations, such as typically having small sample sizes and, especially with regard to the supposedly disturbed brain trajectories in ASD, the non-consideration of age-dependency due to narrow age ranges investigated in each study. In addition, automatized tissue classification for morphometry increases the risk of artifacts influencing study results. Hence model-dependent false positives and negatives are commonplace. In summary, these challenges reduce reliability of the single study and consequently demand the integration of data from several studies in order to identify locations, which consistently display alterations of brain structure. In addition, the current literature on voxel-based morphometry (VBM) studies shows an inconsistent terminology relating to diagnoses and a considerable variation in diagnostic tools used. Thus, a quantitative summary of these studies might help to elucidate whether there exist, on the anatomical level, common findings within the broad construct of autism spectrum disorders. That is, are there brain regions where structural alterations have been consistently in spite of the heterogeneous criteria used to define ASD?

Anatomic likelihood estimation (ALE) [Laird et al., 2005; Turkeltaub et al., 2002] is a quantitative algorithm for the detection of significant convergence among reported coordinates for local maxima of change. This approach treats the reported foci of individual VBM studies not as points but as spatial probability distributions centered at the given coordinates. By computing the union of these probabilities, ALE maps can be computed, which are subsequently compared to the between-study variability using non-parametric inference based on a randomization procedure. Hence, ALE analysis does provide a powerful, observer-independent approach for the meta-analysis of structural (or functional) whole-brain voxel-based studies. Consequently, there is no *a priori* restriction or hypothesis, but rather convergence of findings is assessed across the entire brain. Furthermore, it allows subsequent analysis of the histological location of consistent changes using cytoarchitectural probability maps as microstructural references [Amunts and Zilles, 2001; Eickhoff et al., 2005, 2006a,b,c; Zilles et al., 2002].

We here report results from an ALE-based meta-analysis of 16 morphometric MRI studies using voxel-wise whole-brain VBM analysis, which in total enrolled 277 ASD patients and 303 healthy controls. The purpose of our ALE meta-analysis was to provide a quantitative summary of the existing findings on brain structure changes in autism spectrum disorder and to identify brain regions that are consistently reported to show changes in ASD patients compared to controls in VBM in spite of the variability between studies. After computation of ALE maps, we used the SPM Anatomy Toolbox v1.5 [Eickhoff et al., 2005, 2006a] to histologically allocate the clusters obtained by

ALE using cytoarchitectonic maximum probability maps. We then aimed to depict age-related effects of gray matter and white matter changes.

METHODS

Literature Search and Selection

We conducted a comprehensive search for morphometric studies by Pubmed literature search (www.pubmed.org, search strings: "autism + morphometry," "autism + brain + mri," "autism + brain + voxel-based," "asperger + morphometry," "asperger + brain + mri," and "asperger + brain + voxel-based," "autism + VBM," "asperger + VBM") on structural magnetic resonance imaging (sMRI) studies. The literature cited in systematic reviews and the obtained papers was also assessed to identify additional neuroimaging studies dealing with brain structure changes in autism spectrum disorders not retrieved by the database search. Literature from a publication period from 1999 to 2009 was included.

Only studies that analyzed local changes in gray and/or white matter volume based on structural MR images were included in our meta-analysis. Furthermore, whole-brain results in stereotactic coordinates (Talairach/MNI) (x,y,z) were required for inclusion.

Our search strings identified a total of 593 articles in Pubmed. 566 studies had to be excluded due to one of the following reasons:

- the studies were review articles
- the studies reported only MRI data for animal models
- the studies reported only functional, not structural MRI data for humans
- studies reported only PET data
- studies contained solely diffusion imaging data
- studies contained solely data derived from volumetric, not voxel-wise analysis

Of the remaining 27 articles, 11 studies had to be excluded, because they did not report stereotactic coordinates, did not compare ASD patients with healthy controls, but e.g., ASD patients with ADHD patients or a mixed patient group with healthy controls, or did not report whole-brain results.

Diagnostic criteria for ASD have been diverse over the time and communities covered by the included studies, although standardized tests, especially the Autism Diagnostic Observation Schedule-Generic (ADOS-G; [Lord et al., 2000]) and the Autism Diagnostic Interview-Revised (ADI-R), have been used in many instances. Since it was our aim to give a quantitative overview of ASD literature, we chose to include all studies that were published in peer-reviewed literature as investigating patients with autism or autism spectrum disorder, regardless of the actual mode of diagnosis. That is, while the diagnostic criteria are heterogeneous across the included studies, all were accepted by the scientific community as contributing to the knowledge on the neurobiological substrates of ASD.

Only comparisons between ASD patients and healthy controls were analyzed. Studies were excluded if they (1) did not report stereotactic coordinates of maximal brain structure changes but volumetric results or (2) did not report any comparisons between healthy subjects and ASD patients (but, e.g., only comparisons between ASD patients and another patient group). Also comparisons between a mixed group of e.g., ASD and ADHD patients and a healthy control group were excluded. These criteria yielded a total of 16 peer-reviewed articles available for meta-analysis, jointly reporting on 277 ASD patients and 303 healthy controls (see Table I). In total, these studies reported 283 foci. One hundred and thirty-seven reported foci indicated increased gray matter (GM) or white matter (WM) for ASD patients (128 GM, 9 WM), while the remaining 146 foci indicated the reduced GM or WM in ASD (70 in GM, 76 in WM) (see Table I).

Anatomic Likelihood Estimation Meta-Analysis Procedure

The meta-analysis was carried out using a revised version [Eickhoff et al., 2009] of the activation likelihood estimation (ALE) approach for coordinate-based meta-analysis of neuroimaging results [Laird et al., 2005; Turkeltaub et al., 2002]. This algorithm aims at identifying areas showing a convergence of findings (activations or morphometric changes) across different experiments, which is higher than expected under a spatially random association between the results obtained in the individual studies. The key idea behind ALE is to treat the reported foci not as single points, but rather as centers of 3D Gaussian probability distributions. These reflect the spatial uncertainty associated with each reported set of coordinates and were modeled based on empirical estimates of between-subject and between-template variance. By weighting the former by the number of subjects, this approach considers that larger sample sizes should provide more reliable approximations of a "true" effect and should therefore be modeled by tighter Gaussian distributions yielding more localizing power [Eickhoff et al., 2009].

Most ALE-based studies on neuropsychiatric disorders focus exclusively on gray matter changes [Fornito et al., 2009; Glahn et al., 2008]. Nevertheless, white matter pathologies seem to contribute not only to ASD-specific pathophysiology [Minshew et al., 2007], but, at least in the younger ages, also to brain volume changes [Carper et al., 2002]. Gray matter (GM) and white matter (WM) changes in VBM analyses are intended to reflect volume changes of these two compartments [Ashburner and Friston, 2005]. However, due to different tissue registration parameters,

TABLE I. Overview on the clinical details in the studies included in this meta-analysis

Reference	*n* (ASD patients)	*n* (healthy controls)	mean age (ASD)	mean age (healthy controls)	Foci with GM density or volume increase	Foci with GM density or volume decrease	Foci with WM density or volume increase	Foci with WM density or volume decrease	Gender ratio ASD patients (male/female)	Gender ratio healthy controls (male/female)	Mean IQ ASD sample (if given)	Modulated/unmodulated images	Smoothing kernel	Significance level[a]	Diagnosis of partcipants/diagnosis according to[b]
Abell et al., 1999[114]	15	15	28.75	25.3	6	3	0	0	12/3	12/3	not reported	unmodulated	12 mm FWHM	P(uncorr.) < 0.01	Asperger's syndrome/DSM-IV
Boddaert et al., 2004[115]	21	12	9.3	10.8	0	4	0	2	16/5	7/5	55.8	unmodulated	12 mm FWHM	P(uncorr.) < .001	autism/ADI-R
Bonilha et al., 2008[116]	12	16	12.4	13.2	70	0	0	43	12/0	16/0	not reported, 6 patients described as mentally retarded	modulated	8 mm FWHM	P(corrected on cluster level) < 0.05	autism/DSM-IV, ICD-10
Brieber et al., 2007[117]	15	15	14.2	13.3	2	6	0	0	15/0	15/0	106.8	modulated	12 mm FWHM	P(uncorr.) < 0.001	Asperger's syndrome (13 patients), high functioning autism (2 patients)/ADOS-G, ADI-R
Craig et al., 2007[118]	14	19	37.9	35	0	5	5	3	0/14	0/19	100	modulated	5 mm FWHM	P(corr. on cluster level) < 0.01	Asperger's sydrome (10 patients), autism (4 patients)/ICD-10, ADI-R (for 7 patients), ADOS (5 patients)
Ke et al., 2008[119]	17	15	8.88	9.73	6	1	0	2	14/3	12/3	108.76	modulated	8 mm FWHM	P(uncorr.) < .001	high functioning autism/DSM-IV, ADI-R, CARS
Kwon et al., 2004[120]	11	13	13.5	13.6	3	0	0	0	11/0	13/0	not reported	unmodulated	8 mm FWHM	P(corr. on cluster level) < 0.001	Asperger's syndrome/DSM-IV, ADOS-G, ADI-R
McAlonan et al., 2002[121]	21	24	32	33	0	17	4	0	19/2	22/2	IQ reported to be "in normal range"	modulated	not reported	P(corr. on cluster level) < 0.001	Asperger's syndrome/ICD-10, ADI (18 patients)
McAlonan et al., 2005[122]	17	17	12	11	0	13	0	2	16/1	16/1	101	unmodulated	4.4 mm FWHM	P(corr. on cluster level) < 0.002	autism/ICD-10, ADI-R
McAlonan et al., 2008[123]	33	55	11.6	10.7	0	9	0	0	27/6	47/8	113.2	not reported in detail	not reported in detail	P(corr. on cluster level) < 0.029	Asperger's syndrome and high functioning autism/ADI-R

TABLE I. (Continued)

Reference	*n* (ASD patients)	*n* (healthy controls)	mean age (ASD)	mean age (healthy controls)	Foci with GM density or volume increase	Foci with GM density or volume decrease	Foci with WM density or volume increase	Foci with WM density or volume decrease	Gender ratio ASD patients (male/female)	Gender ratio healthy controls (male/female)	Mean IQ ASD sample (if given)	Modulated/unmodulated images	Smoothing kernel	Significance level[a]	Diagnosis of partcipants/diagnosis according to[b]
Rojas et al., 2006[124]	24	23	20.79	21.41	9	4	0	0	24/0	23/0	94.96	modulated	8 mm FWHM	P(uncorr.) < 0.01	autism/DSM-IV, ADI, ADOS
Salmond et al., 2005[125]	14	18	12.9	12.6	16	2	0	0	13/1	6/12	102	unmodulated	12 mm FWHM	P(FDR-corr.) < 0.05	Asperger's syndrome, (11 patients) high functioning autism (3 patients)/ASAS
Salmond et al., 2007[126]	22	21	12.5	12.0	4	6	0	0	19/3	20/1	102 (high intelligence cohort) and 76) low intelligence cohort	unmodulated	12 mm FWHM	P(FWE-corr.) < 0.05	autism spectrum disorder/ASAS, ABC
Schmitz et al., 2006[127]	10	12	38	39	5	0	0	0	10/0	12/0	105	unmodulated	10 mm FWHM	P(uncorr.) < 0.001	Asperger's syndrome (8 patients), high functioning autism (2 patients)/ICD-10, ADI (7 patients)
Waiter et al., 2004[128]	16	16	15.4	15.5	7	0	0	0	16/0	16/0	100.9	modulated	12 mm FWHM	P(corr. on cluster level) < 0.1	autism spectrum disorder/ADI-R, ADOS-G
Waiter et al., 2005[129]	15	16	15.2	15.5	0	0	0	24	15/0	16/0	100.6	modulated	12 mm FWHM	P(FDR-corr.) < 0.05	autism spectrum disorder/ADI-R, ADOS-G
Total	277	307			128	70	9	76							

[a]If not reported otherwise, significance levels are reported on whole brain-level.
[b]Terminology given as used in the original articles.

volume reductions of the cerebral cortex can be reflected as gray matter volume reductions in one study, but as white matter volume enlargement in another. We therefore also include foci reporting white matter densities in our analysis. Furthermore, as already mentioned, brain structure abnormalities in ASD patients are most likely not static, but subject to age-dependent changes. These findings have led to the hypothesis of disturbances in brain growth trajectories as a key pathophysiological feature in ASD with early brain overgrowth followed by volume reductions [Courchesne et al., 2007]. Given that an identical brain region might possibly be enlarged in younger patients, while being of reduced size in older ones, we regarded it as most appropriate to integrate both foci reporting increases and decreases of gray matter (GM) or white matter (WM) in our analysis. Thus, we intended to identify brain regions displaying structural disturbances (either overgrowth, atrophy or both) in ASD patients.

Consequently, the probabilities of all foci reported in a given study (independently of analyzed tissue and contrast) were combined for each voxel, resulting in a modeled anatomical effects (MA) map (paralleling the modeled activation maps in functional imaging meta-analyses). Taking the union across these MA-maps yielded voxel-wise ALE scores describing the convergence of results at each particular location. To distinguish "true" convergence between studies from random convergence, i.e., noise, these ALE scores were subsequently compared to an empirical null-distribution derived from a permutation procedure. This null-distribution should reflect a random spatial association between experiments, but regard the within-experiment as a fixed property. Hereby, a random-effects inference is invoked, focusing on inference on the above-chance convergence between different experiments, not the clustering of foci within a particular experiment. Computationally, deriving this null-hypothesis involved sampling a voxel at random from each of the MA-maps and taking the union of these values in the same manner as done for the (spatially contingent) voxels in the true analysis. The "true" ALE scores were then tested against these ALE scores obtained under the null-distribution. Precisely, the *P*-value of each "true" ALE was computed as the proportion of equal or higher random values. The resulting non-parametric *P*-values were then transformed into *Z*-scores and thresholded at a cluster level corrected threshold of $P < 0.05$ [Ashburner and Friston, 2005].

Additionally, we performed analyses for gray and white matter increases and decreases separately, following the above mentioned protocol. For these separate analyses, we used a cluster forming threshold of $P < 0.01$ (uncorrected).

Anatomical Allocation by Probabilistic Maps

We used the SPM Anatomy Toolbox v1.5 [Eickhoff et al., 2005, 2006a,b,c], to compare the localization of the obtained significant effects to histological areas as described in probabilistic cytoarchitectonic maps and summarized it in a maximum probability map. A maximum probability map (MPM) is a summary map of different histological maps. It is based on the idea of attributing each voxel of the reference space to the most likely cytoarchitectonic area or the most likely myeloarchitectonically defined fiber-tract (see Table II) at this position. MPMs thus allow the definition of non-overlapping representations of all areas from a set of inevitably overlapping probabilistic maps [Eickhoff et al., 2005; Naito et al., 1999; Tzourio-Mazoyer et al., 2002].

TABLE II. Overview over the cytoarchitectonic probabilistic maps and the probabilistic fibre maps used by the Anatomy Toolbox v1.5

Anatomical region	Reference
Cortical regions	
Broca's region (BA 44, BA 45)	Amunts et al.1999[130]
Inferior parietal areas (PFop, PFt, PFcm)	Caspers et al. 2006, 2008[131,132]
Intraparietal areas (hIP1, hIP2)	Choi et al. 2006[133]
Premotor cortex (BA 6)	Geyer 2004[134]
Somatosensory area BA 2	Grefkes et al. 2001[135]
Visual areas V1, V2	Amunts et al. 2000[136]
Visual area V5	Malikovic et al. 2007[137]
Visual area V3v	Rottschy et al. 2007[138]
Superior parietal areas 7A, 7PC, intraparietal area hIP3	Scheperjans et al. 2008a,b[139,140]
Fibre tracts	
Corticospinal tract	Bürgel et al., 1999, 2006[141,142]
Optic radiation	
Acoustic radiation	
Fornix	
Cingulum	
Corpus callosum	
Superior longitudinal fascicle	
Superior and inferior occipitofrontal fascicle	
Uncinate fascicle	

For all clusters in gray matter regions that have not yet been histologically examined, we used the Harvard Cortical and Subcortical structural atlas [Kennedy et al., 1998; Makris et al., 1999] as part of FSLview v3.0. Clusters in white matter regions not yet covered by probabilistic fiber tract mapping were anatomically labeled using the JHU White-Matter Tractography atlas [Wakana et al., 2004] also as part of FSLview v3.0.

The Influence of Age on Gray Matter/White Matter Changes

We aimed to depict age effects on gray and white matter changes. Since age ranges or standard deviations were not consistently reported across studies only mean age-values were used for correlations. Age-related differences

TABLE III. Localization of the significant clusters of convergence

Coordinates	*k*	Anatomic localization	Analysis by cytoarchiterctural MPMs/Harvard cortical and subcortical structural atlas/JHU White-Matter Tractography atlas
46, −62, −2	238	Right occipital lobe	V5
−32, −36, 60	78	Left pericentral region	4p, 3b, 2
8, 18, −2	40	Right caudate	Right caudate
32, −8, 20	26	Proximate to the right parietal operculum	White matter proximate to the right parietal operculum
40, −22, −8	30	Right medial temporal lobe	Inferior fronto-occipital fascicle/ inferior longitudinal fascicule /hippocampus
−26, 6, 0	28	Left putamen	Left putamen

between ASD patients and controls that were congruent between gray and white matter (indicative of absolute overgrowth or atrophy of this region) and those changes that showed inverted relations between age-related changes of gray and white matter (indicative of changes in the relation between gray and white matter), respectively, were assessed in two separate analyses. First, we investigated whether gray matter and white matter changes in ASD patients both unidirectionally contributed to the clusters of convergence (e.g., whether gray matter reduction was accompanied by white matter reduction) by correlating the contribution of each study modeled anatomical effect map to the respective cluster. Here the contribution was defined as the integral of the Gaussian distribution representing the respective focus across all voxels making up the assessed cluster.

Changes in gray matter, however, do not necessarily have to go along with equivalent changes in white matter. Disturbed trajectories, for example, can lead to cortical atrophies accompanied by white matter overgrowth and vice versa. Therefore, to check for inverted correlations between GM and WM density values, an analogous model was calculated using inverted values for white matter density changes.

RESULTS

Regions With Significant Differences in Gray and White Matter Density Between ASD Patients and Control Subjects

We found six clusters showing significant convergence of VBM findings (see Table III, Fig. 1). The largest cluster was located in the right lateral occipital lobe (46, −62, −2; $k = 238$). Allocation by cytoarchitectural maximum probability maps as implied in the Anatomy Toolbox v1.5 [Eickhoff et al., 2005, 2006a,b] showed its position mainly in the right area V5. This cluster extended to the right inferior temporal lobe as well as into the occipital white matter. The second largest cluster was observed in the superior part of the left central sulcus (−32, −36, 60; $k = 78$), mainly situated in areas BA 4b and BA 3b. A smaller part of the cluster was located in BA 2. Two clusters were located in the basal ganglia: one in the right caudate (8, 18, −2; $k = 40$) and another in the left putamen (−24, 6, 0; $k = 28$). Also, the right medial temporal lobe (40, −22, −8; $k = 30$) showed changes: the inferior fronto-occipital fascicle and the inferior longitudinal fascicle were at the center of this cluster. Parts of this cluster were also located in the CA1 area of the hippocampus. Finally, converging evidence for volumetric changes in the region of the right superior insula and the adjacent parietal operculum (32, −8. 20; $k = 26$) were detected.

In an analysis separately on gray matter increases and decreases, we found GM decreases in the left putamen, bilaterally in the cerebllar vermis, the left hippocampus/ amygdala, the left operculum, the left superior medial gyrus, the right middle temporal gyrus, the left precentral gyrus and the right putamen. GM increases were detectable in both the right and the left temporooccipital region (allocation by cytoarchitectonic probabilistic mapping: V5), the right precuneus, the right cerebellum, a cluster in the right lingual gyrus and the right inferior occipital gyrus and a cluster in the left cerebellum. WM decreases were found in a cluster adjacent to the medial anterior cingulated gyrus. We did not find any clusters of convergence for WM increases (see Supporting Information Table I).

Evidence for Age Effects on Gray and White Matter Changes

We then aimed to depict for each of the significant clusters age-related effects on gray matter and white matter changes (see Fig. 2a–c). Most studies contributing to the cluster in the V5 area reported increased GM in ASD patients, however, effects decreased with age and there was a reduction of GM in the oldest group. The only study reporting WM changes in this area described a WM decrease in pre-adolescent ASD patients.

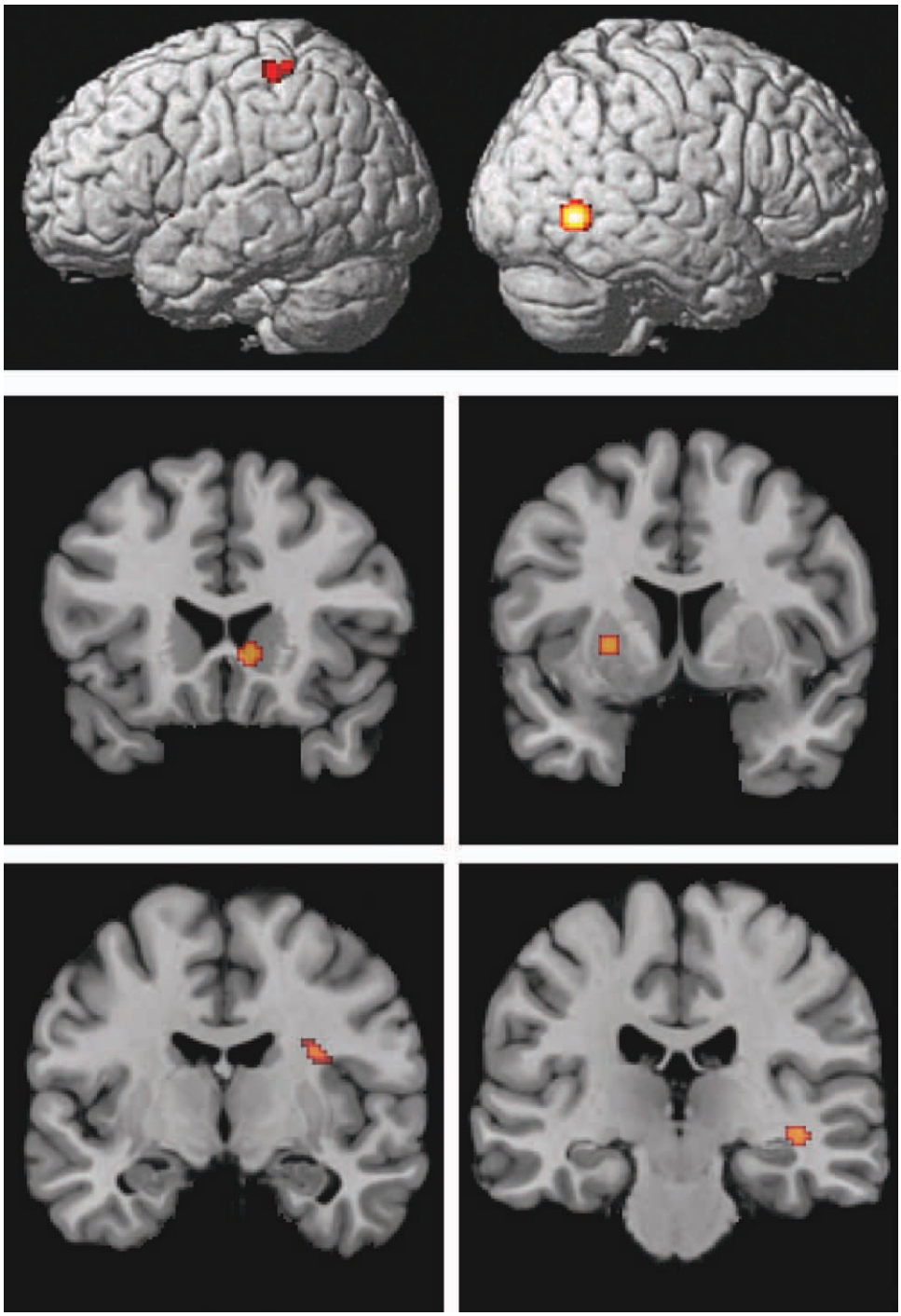

Figure 1.

Significant clusters of convergence obtained by ALE-based analysis indicating locations in the lateral occipital lobe, the pericentral region, the medial temporal lobe, the basal ganglia and proximate to the right parietal operculum. Both foci indicating gray and white matter changes were included in this model. Since disturbances in brain growth trajectories were discussed as a key pathophysiological feature in ASD, we integrated both foci reporting increases and decreases of gray matter (GM) or white matter (WM) in our analysis. Thus, the depicted clusters indicate brain regions consistently altered in ASD patients. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

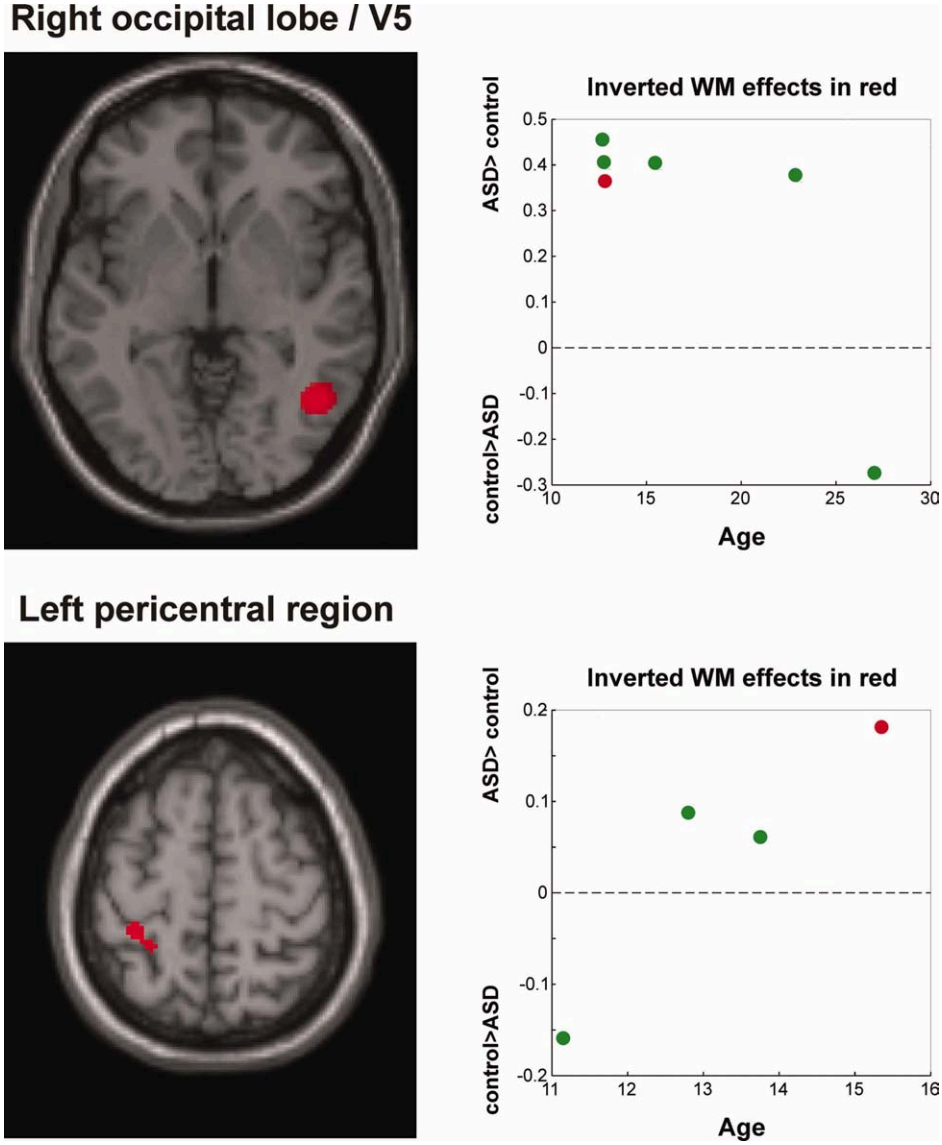

Figure 2.

Gray matter (GM) and white matter (WM) changes, as reported in individual studies and their relationship to age in the significant clusters identified by ALE-based analysis. Each of the significant ALE clusters was analyzed separately for age effects on gray and white matter changes. Mean age-values were used for correlations. The contribution was defined as the integral of the Gaussian distribution representing the respective focus across all voxels making up the assessed cluster. GM changes: green dots, WM changes: red dots. **a** Age-dependent changes of GM (green) and WM (red) densities in the right occipital lobe and the left pericentral region. **b** Age-dependent changes of GM (green) and WM (red) densities in the right caudate nucleus and the left putamen. **c** Age-dependent changes of GM (green) and WM (red) densities in the right medial temporal lobe and the right parietal operculum. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In contrast, our results for GM in the pericentral region depicted an age-dependent increment. Young ASD patients were reported to have decreased GM compared to healthy controls, but after the onset of puberty, ASD patients showed higher GM than the control group. Moreover, one study reported decreased WM in post-pubertal ASD patients.

The changes in the right caudate showed a similar pattern. Pre-pubertal GM was reported to be decreased in ASD patients. However, after puberty ASD patients showed higher GM than normal controls, while WM density was reduced. In contrast, an age-dependency was not detectable for changes in the left putamen. GM was

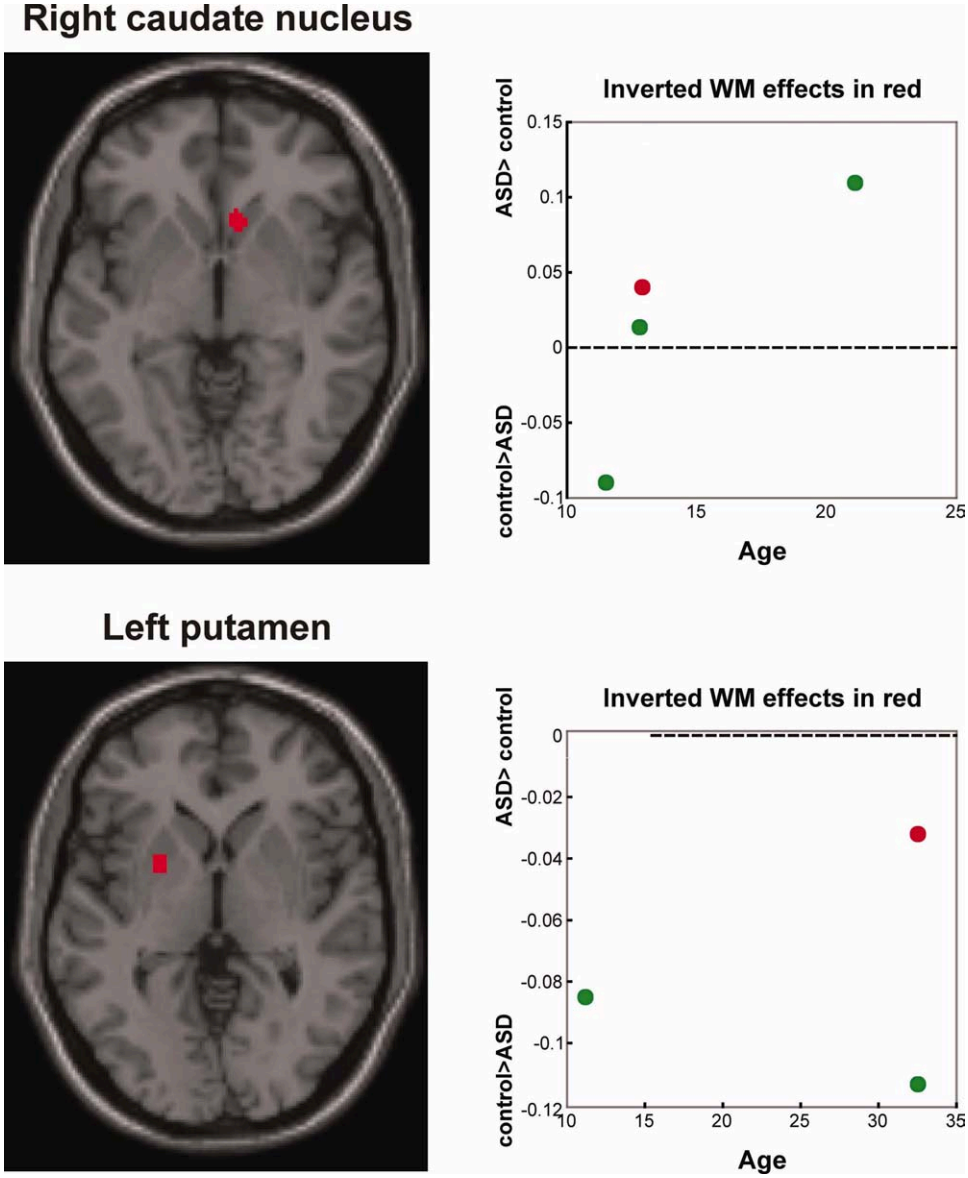

Figure 2.

reduced both pre- and post-puberty with increased WM. Hence, there was no common pattern for the findings in the basal ganglia.

Our approach found evidence for age-related changes in the region adjacent to the superior insula and the parietal operculum in VBM findings. Pre-adolescent GM was increased in ASD patients, but was decreased in adult autistics compared to healthy controls. WM, however, showed a mirror-like pattern with pre-adolescent decreases and increases in adults. Also in the medial temporal lobe, GM seemed to be subject to age-related changes with young infants displaying decreased GM, while puberty seemed to go along with increases in GM. Post-pubertal WM was decreased, though.

DISCUSSION

The etiopathogenesis of autism spectrum disorders still remains to be clarified, but imaging and histopathological studies indicate that brain structure anomalies play an important role [Brambilla et al., 2003; Courchesne et al., 2007; Hrdlicka, 2008; Minshew et al., 2007]. We here presented a meta-analysis of 16 whole-brain VBM studies

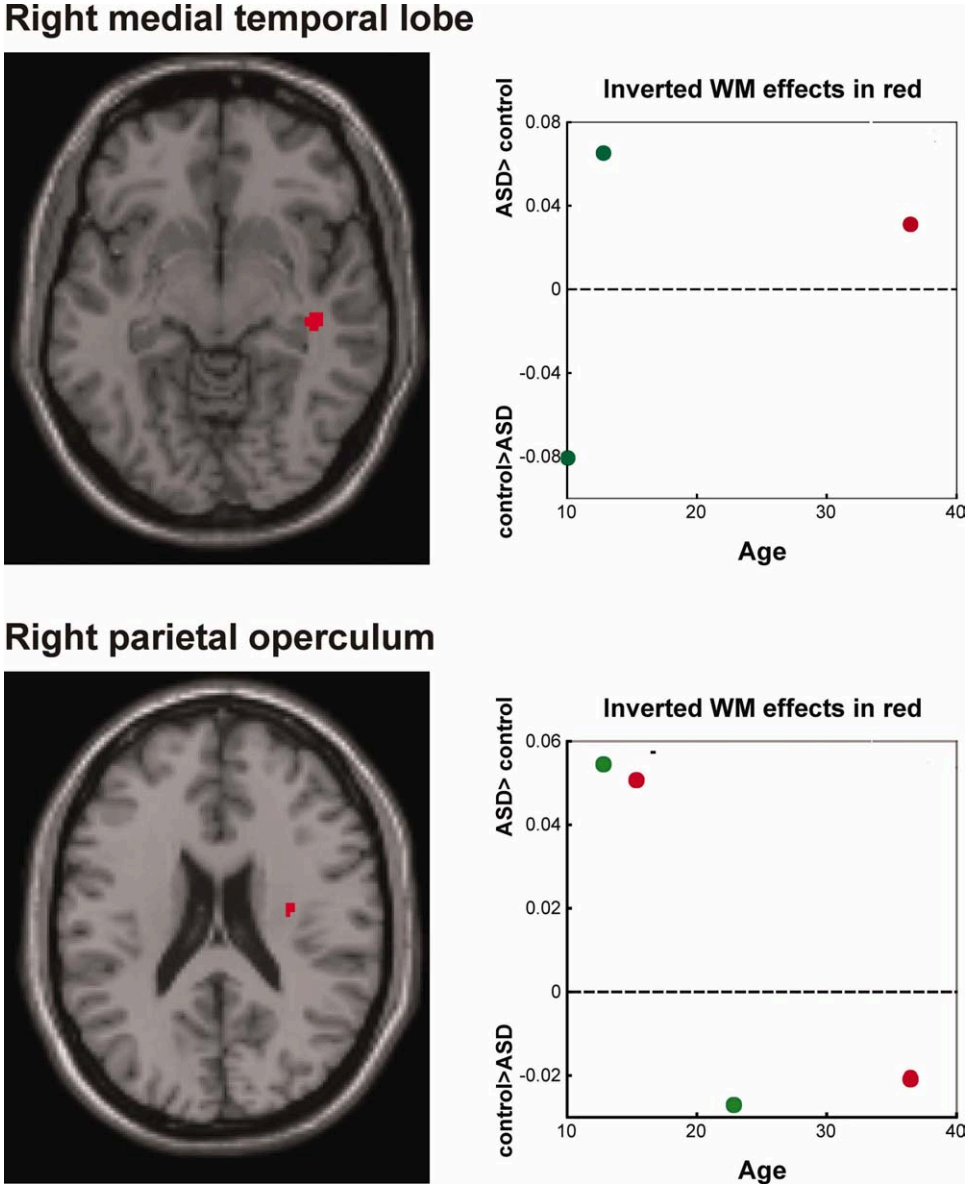

Figure 2.

using anatomic likelihood estimation. We chose voxel-wise whole-brain analyses, since these studies do not require an *a priori* hypothesis and are more sensitive to localized brain structure changes. This is the first quantitative meta-analysis on whole-brain brain structure anomalies in ASD patients as reported in voxel-based morphometry studies.

The studies included in our meta-analysis jointly report on brain structure differences between 277 ASD patients and 307 healthy controls. Mean age of the study samples ranged from 8.88 years [Ke et al., 2008] to 38 years [Schmitz et al., 2006] for ASD patients and from 9.73 years [Ke et al., 2008] to 39 years [Schmitz et al., 2006] for healthy controls. Sample sizes of the included studies were comparatively small for structural imaging studies (11 ASD patients as the smallest sample size [Kwon et al., 2004], 33 ASD patients as the largest patient cohort [McAlonan et al., 2008]). Given this, our meta-analysis aims to critically summarize the findings of these studies in a quantitative fashion and to test whether additional insight into age-related brain structure changes might be derived.

Significant clusters of convergence were found in the right occipital lobe (anatomical allocation by probabilistic

maps: V5), the left pericentral region (*4p, 3b, 2*), the right caudate, proximate to the right superior insula and the parietal operculum, the left putamen and in the right medial temporal gyrus (inferior fronto-occipital fascicle/inferior longitudinal fascicle/hippocampus).

Lateral Occipital Lobe/V5

V5 is a motion sensitive area of the visual cortex located on the lateral hemispherical convexity near the junction of the lateral occipital sulcus and the ascending part of the inferior temporal sulcus [Watson et al., 1993; Wilms et al., 2005]. The human visual system is broadly organized into two segregated pathways [Mishkin et al., 1982]. The ventral—or parvocellular—stream includes areas of the temporal cortex and is involved in object vision and color perception. The dorsal—or magnocellular—stream, in contrast, includes areas of the posterior parietal cortex and is involved in spatial viewing and motion perception but also action observation [(Merigan and Maunsell, 1993; Merigan et al., 1991; Mishkin et al., 1982)]. V5 is part of the latter pathway [Goebel et al., 1998; Wang et al., 1999]. Some neurons in V5 reacts to stimuli moving over comparatively large sections of the visual field [Dakin and Frith, 2005], while another is reacting to the contrast between the direction of a moving object and its background [Tootell et al., 1995].

Several studies have indicated that visual perception in ASD patients differs from that of healthy controls. ASD patients display superior performance on tasks necessitating the detection of a static visual target embedded in a larger field [Caron et al., 2004; Pellicano et al., 2005; Plaisted et al., 1990], and they are more detail-oriented [Jolliffe et al., 1997; Lahaie et al., 2006; Mottron et al., 1999; Shah and Frith, 1983, 1993]. In contrast, patients are consistently less sensitive to a variety of complex motion stimuli, such as biological motion stimuli or random dot kinematograms [Bertone et al., 2003; Blake et al., 2003; Gepner et al., 1995; Milne et al., 2002; Spencer et al., 2000]. Also, their motion coherence threshold is increased [Milne et al., 2002; Spencer et al., 2000]. These dichotomous findings on visual processing led to the hypothesis of impaired functioning either of motion processing per se [Gepner et al., 1995] or of the dorsal stream [Blake et al., 2003; Milne et al., 2002; Spencer et al., 2000]. Because of the involvement of the V5 region in motion processing, our results of brain structure alterations in this area in ASD patients might partly explain these pathophysiological findings.

Remarkably, in our analysis on GM and WM changes separately, GM increases were found bilaterally in that brain area. These findings are further hints for a role of V5 in ASD-related pathophysiology.

Pericentral Region/4p, 3b, 2

The second largest cluster found by our meta-analysis was located pericentrally in both areas 3b and 4. Area 3b is part of the postcentral somatosensory cortex and receives its afferents as a primary somatosensory region mainly from the ventral posterior nucleus (face representation) and from the ventral posteromedial nucleus (representation of body stem and limb) of the thalamus [Young et al., 2003]. This is consistent with activation-likelihood analyses of functional imaging in ASD populations that have shown atypical activations in somatosensory areas including the postcentral gyrus [DiMartino et al., 2009]. Area 4p is a subdivision of the human motor cortex that differs both cytoarchitectonically, neurochemically and functionally from its anterior counterpart, area 4a [Geyer et al., 1996]. All of these areas are crucial for sensorimotor functions [Naito et al., 2000]. Sensorimotor deficits in ASD patients have been well described [Bernabei et al., 2003; Mandelbaum et al., 2006; Takarae et al., 2008; Tuchman et al., 1991]. Changes in the primary somatosensory and motor cortices therefore might well be regarded as a neural correlate of these disturbances.

Support for this hypothesis of alterations in the primary somatosensory cortex comes from neurophysiological data. A recent study using magnetoencephalography to determine the precise location of cortical somatic maps found abnormalities in the organization of sensory representations in the brains of ASD patients [Coskun et al., 2009]. These electrophysiological findings might reflect not only functional, but also structural changes in the postcentral gyrus. Furthermore, a study on cortical thickness in ASD patients found alterations in the face area of the postcentral gyrus [Hadjikhani et al., 2006]. Though it has to be noted that only a small part of the sensorimotor areas in the brain was shown to be affected in this study, it involved the hand representation in healthy subjects. Further studies on somatic maps might help to identify whether ASD is the cause of pronounced changes in this region. We would, however, speculate, that the observed findings relate to the reduced motor repertoire and the impaired sensorimotor functions ("clumsiness") of ASD patients.

Basal Ganglia

Alterations were found in the basal ganglia, namely the left putamen and the right caudate. Alterations of the basal ganglia, especially the caudate nuclei, have been repeatedly described in ASD patients and were often found to correlate with impaired motor performance or repetitive and stereotyped behavior [Hardan et al., 2003; Langen et al., 2007; Sears et al., 1999; Stanfield et al., 2008].

Retrograde transneural transport of the herpes simplex virus has helped to elucidate the connectivity between the caudate nuclei and other brain regions. The caudate receives its input primarily from frontal, inferior parietal, pre-occipital and medial temporal areas, mainly the amygdala, the hippocampus and the parahippocampal gyrus [Alexander et al., 1986]. With reference to their

neurophysiological relevance, the connectivity of the caudate has been segregated into circuits. The caudate is associated with associative, lateral orbitofrontal and orbitofrontal circuits [Alexander et al., 1986; Tisch et al., 2004], thus linking the caudate to sensorimotor skill learning, but also to executive processes [Alexander et al., 1986; Posner and DiGirolamo, 2000]. Functional connectivity between the caudate and the cerebral cortex has been shown to be impaired in ASD patients [Horwitz et al., 1988; Turner et al., 2006]. The hypothesis of a contribution of basal ganglia anomalies to behavioral stereotypes is further supported by findings of basal ganglia anomalies, mainly of the caudate, in obsessive-compulsive disorder [Atmaca et al., 2007; Whiteside et al., 2004].

A meta-analysis of volumetric studies describes an enlargement of the right caudate [Stanfield et al., 2008] in ASD patients, which closely matches our findings. Hence, this convergence between volumetric and VBM data adds further support to the important role that the caudate nucleus may play in the pathophysiology of autism. Notably, in contrast to the positive correlation of GM overgrowth with age in the right caudate, we did not find any age-related effects of left putamen. These findings suggest complex disturbances of basal ganglia trajectories.

Besides its potential involvement in behavioral stereotypes, the basal ganglia have been implicated in the interpretation of emotional body language. The putamen and the striatum have been shown to interact with the superior colliculus, the pulvinar, and the basolateral amygdala as a fast primary network in response to emotional body language [de Gelder, 2006]. Moreover, the putamen has been shown to have lower glucose metabolism in ASD patients than in neurotypical controls [Haznedar et al., 2006]. Total putamen volume was also found to correlate positively with repetitive behavior [Hollander et al., 2005]. Thus, pathologies of the basal ganglia circuitry seem to be involved in both pathologies of the motor and of the emotion processing systems.

Medial Temporal Lobe

Volumetric studies frequently have found anomalies of the medial temporal lobe of ASD patients [Carper et al., 2002; Penn, 2006]. Functional neuroimaging has highlighted the role of impaired medial temporal lobe functioning in face recognition [Pierce et al., 2004, 2001] and processing of emotional facial expressions [Baron-Cohen et al., 1999; Dalton et al., 2005]. These deficits might be key players in ASD pathophysiology. Altered activations of the amygdala were among the most consistent findings [Baron-Cohen et al., 1999; Dalton et al., 2005, DiMartino et al., 2009; Pierce et al., 2001]. However, structural alterations of the amygdala were less frequent than functional imaging results led us to expect. A meta-analysis on volumetric studies showed an age-volume interaction for the amygdala, but no consistent changes of the amygdalae over all ages. Although we found a cluster of convergence in the right medial temporal lobe, this cluster did not include the amygdala.

The hippocampus [Schumann et al., 2004] has been shown to be volumetrically altered in ASD patients, but findings were inconsistent with a variety of studies reporting no alterations of the hippocampus [Palmen et al., 2006; Zeegers et al., 2008]. The second gray matter structure within the cluster was the ID1 area of the insula. Cortical folding analysis revealed abnormalities of the folding patterns of the anterior insula [Nordahl et al., 2007]. Our findings here underscore the need for further studies on this region.

Changes at the Insula/Parietal Operculum

ASD-related pathologies in the region of parietal operculum were less frequently reported. Nordahl et al., however, reported sulcal depth differences between ASD patients and neurotypical controls in the left frontal and bilaterally in the parietal operculum [Nordahl et al., 2007]. Another study on gyrification also found depth differences in the parietal operculum [Levitt et al., 2003]. Given the location of the cluster maximum and the fact that half of the foci contributing to this cluster were referred to WM, we interpret these findings as most likely caused by white matter anomalies. The region closest to these changes is the OP3 region. Functional imaging has shown that this region is somatosensory in nature and most likely contains a somatotopic map [Eickhoff et al., 2006b,c]. The operculum (and OP3 as a subdivision) is implicated in a variety of complex functions related to multimodal sensory and motor integration [Caselli, 1993]. Thus, the changes observed might be an indicator of different anatomic connectivity of the parietal operculum in ASD patients that may underlie impairments in multisensory integration.

Findings of Volumetric Studies and the Results of This Meta-Analysis

A consistent hypothesis on neuroanatomic changes in ASD does not yet exist. Most volumetric MRI studies have described increases in the frontal, temporal and parietal lobes of ASD patients [Amaral et al., 2008; Carper et al., 2002; Courchesne et al., 2007; Hazlett et al., 2006; Herbert et al., 2004; Palmen et al., 2005]. Rater-dependent MRI studies enrolling toddlers and infants and aiming to quantify gray matter abnormalities have repeatedly described an anterior–posterior gradient of anomalies with the frontal and the temporal lobe as most affected [Bloss and Courchesne, 2007; Carper et al., 2002; Hazlett et al., 2005; Kates et al., 2004; Palmen et al., 2005]. Our results could not confirm this hypothesis of an anterior–posterior gradient in brain structure anomalies in ASD at least in the patient populations on which VBM findings have been

reported up to now. Contrarily, the two largest clusters of convergence were located in the lateral occipital and in the postcentral parietal cortex, while only three smaller clusters were situated in the frontal or temporal lobe. Though, three of these rater-dependent studies [Bloss and Courchesne, 2007; Carper and Courchesne, 2005; Kates et al., 2004] had much younger ASD samples than the studies included in this meta-analysis.

Two differences in the study settings might provide possible explanations for this discrepancy: methodical differences between whole-brain voxel-based morphometry and volumetric studies. VBM is based upon the voxel-wise analysis of local GM or WM specific volumes [Ashburner and Friston, 2000], while volumetric studies usually compare the overall volumes of either automatically or hand-drawn pre-defined brain regions. Thus, the former type of studies is more sensitive to regionally limited changes of brain structure [Ashburner and Friston, 2000] that might be too confined to cause a significant effect on the total volume of a comparatively large region, such as a brain lobe or total gray matter. Volumetry, in contrast, is more sensitive to small, but consistent changes over all voxels of a given VOI. Analogous methodical differences come into play when comparing the results of rater-dependent studies with those of VBM studies.

Besides these methodical considerations, the differences in age groups must be considered. As already discussed, brain structure anomalies in ASD might be age-dependent due to different brain growth trajectories. Both volumetric studies [Bloss and Courchesne, 2007; Carper and Courchesne, 2005; Hazlett et al., 2005; Kates et al., 2004] and the VBM results included in this meta-analysis cover diverse age groups from childhood to adulthood (see Table I). As shown by our correlation analysis, almost all regions that show significant convergence of VBM findings also show age effects with the result that there may be reduced volumes in younger and overgrowth in older patients. That is, for the same region the differences between ASD patients and controls may point in either direction depending on the investigated age group. Consequently, age-related effects on brain anomalies and the age of the included patients might represent an important factor for the inter-study variance and hence the heterogeneous literature.

Hints at Complex Disturbances of Brain Growth in ASD

We also aimed to investigate whether there were age-dependent changes of brain growth patterns in ASD patients. Because of the fact that only three to six data points contributed to each cluster, correlation analyses did not seem appropriate. Visually, at least four out of the six significant clusters (located in the right V5 area, the left pericentral region, the right caudate and the right parietal operculum) appeared to display age-dependent changes of GM and WM. Remarkably, puberty and early adolescence appeared to emerge as a potential turning point of age related differences, with previous regional brain overgrowth turning into atrophy and vice versa [Paus et al., 2008].

Puberty and adolescence are known to be phases during which a variety of brain structure changes take place [Lenroot and Giedd, 2006; Paus et al., 2008]. Volumes of cortical gray matter in healthy subjects, for instance, increase during childhood, reaching peak levels at approximately the onset of puberty and then gradually decline in the frontal and in the parietal lobes [Giedd et al., 1999]. White matter, in contrast, shows a rather clear linear increase throughout childhood and adolescence, with the maximum volumes often reached as late as the third decade of life [Pfefferbaum et al., 1994]. Changes in synaptic pruning and myelination are frequent explanations for these findings of brain structure changes in adolescence [Huttenlocher, 1984; Huttenlocher and de Courten, 1987], but changes in neural connectivity have been discussed as well [Paus et al., 2008].

In this context, our findings suggesting puberty as a watershed for regional overgrowth and atrophy patterns further hint at disturbed brain maturation processes in ASD patients. These disturbances seem to emerge in early childhood and to persist over the whole life of patients. Notably, in the affected brain regions, these changes do not appear unidirectional in the sense of a unanimous atrophy or overgrowth, but rather suggest a desynchronization of growth between the altered structures and the rest of the brain.

A variety of longitudinal and cross-sectional volumetric studies have gathered convincing evidence for abnormal trajectories in ASD patients with early brain overgrowth at 1–2 years of age and a narrowing of the brain volume differences between patients and healthy controls during later childhood and adolescence [Bartholomeusz et al., 2002; Courchesne et al., 2003; Dawson et al., 2007; Dementieva et al., 2005; Dissanayake et al., 2006; Hazlett et al., 2005; Redcay and Courchesne, 2005]. A recent longitudinal volumetric study by Schumann and colleagues enrolling a total of 41 toddlers and 44 typically developing controls found a significant abnormal growth rate for frontal, temporal, parietal and cingulate gray matter between 1.5 and 5 years of age [Schumann et al., 2010]. In addition, findings of a recent VBM study of more than 50 ASD patients also hint at the congruent presence of regions with left- and right shifted, respectively, growth curves [Greimel et al., under review]. The marked changes in brain structure during puberty and adolescence, requiring detailed adjustment of brain maturation between the different telencephalic regions are obviously not retraced in several regions of the autistic brain.

Hence, the illustrative findings of our study are consistent with the quantitative findings of previous longitudinal and cross-sectional studies. We regard our findings as an additional hint at complex disturbances of brain growth trajectories of ASD patients as suggested by a variety of volumetric studies. These disturbances, resulting in structural and

functional disconnectivity of several pivotal brain regions, might partly explain ASD-related pathophysiology.

The rather small number of data points contributing to each cluster has to be regarded as a major limitation of these findings. Thus, hints at disturbed trajectories found by our study have to be regarded only as preliminary.

Methodological Issues

There are several limitations to this study. Though characterized by a triad of core symptoms, autism spectrum disorders can vary significantly in their clinical presentation [Volkmar and Pauls, 2003]. This could mean that different neurobiological pathomechanisms might underlie the diagnosis of ASD in different patients. Studies enrolled in our meta-analysis diagnosed ASD on the criteria of ICD-10 [Craig et al., 2007; McAlonan et al., 2002, 2005; Schmitz et al., 2006] or DSM-IV [Abell et al., 1999; Boddaert et al., 2004; Ke et al., 2008; Kwon et al., 2004; Rojas et al., 2006; Waiter et al., 2005]. Two studies enrolled patients that fulfilled both ICD-10 and DSM-IV criteria [Bonilha et al., 2008; Brieber et al., 2007]. Two studies [Salmond et al., 2005, 2007] used the Australian Scale for Asperger's syndrome for their diagnosis, while two others used the ADI-R [McAlonan et al., 2008; Waiter et al., 2004]. Although all of the diagnostic scales used include a rating of the three autistic core symptoms, diagnostic criteria do vary among scales. Thus, the patient samples included have to be regarded as clinically heterogeneous apart from the major symptoms and might have heterogeneous changes in neuroanatomy. The same holds true for the fact that some studies also included patients with intelligence impairments, while others did not. Since only a comparatively small number of published studies matched inclusion criteria (in particular, whole-brain VBM comparison between patients and controls), we were not able to perform separate analyses on diagnostic subgroups or subgroups defined by the diagnostic tools used. Thus, more detailed analyses on structural findings pertaining to diagnostic subgroups of autism spectrum disorders will be an important topic for future research, once more whole-brain based VBM studies on this population are available.

Various methodological factors can influence the outcome of a VBM study, such as acquisitional (e.g., scanner platform, field strength, imaging sequences, image acquisition parameters) and analysis details (e.g., segmentation parameters, smoothing, use of modulated or unmodulated images, etc.), Studies included in this meta-analysis span over a period of nearly 10 years. Consequently, imaging and analysis techniques employed in these studies also reflect technical developments in these fields. It is one of the great advantages of ALE-based meta-analyses that they provide a powerful tool to integrate these results in order to assess whether published results do converge on certain brain regions despite these methodical differences, hinting at consistent neuroanatomical changes in ASD patients. That is, it is one of the main benefits of quantitative meta-analysis to pool over acquisition and analysis methods and identify converging evidence for structural alterations.

In this analysis, we chose to jointly analyze GM and WM changes. Once a higher number of studies is available, separate analyses on GM and WM changes seem to be a promising goal for further analyses. Especially the right V5 area and the left putamen were consistent foci of changes in both analyses, while our supplementary analysis showed GM increases also in the left V5 area. However, we do regard the depicted approach as a viable tool for data analysis when only few studies can be included.

Probabilistic cytoarchitectonic maps provide a viable tool for the microanatomical interpretation of both functional and structural MR imaging data [Toga et al., 2006]. Since each voxel of the reference space is attributed to the most likely cytoarchitectonic area or the most likely myeloarchitectonically defined fiber-tract at this position, a probabilistic assignment of a given cluster to those putative microstructural changes that are most likely underlying these macroscopic changes is possible. Because the ALE approach is explicitly aiming to reflect spatial uncertainties of the original data sets by treating foci not as single points, but rather as centers of 3D Gaussian probability distributions, a probabilistic allocation to microstructural areas seems the best fitting approach. Thus, it has to be emphasized that localization by probabilistic cytoarchitectonic maps does not provide an exact histological position of a given focus or cluster, but determines which microstructure is most likely present at a certain position. Furthermore, all factors causing spatial uncertainty such as e.g., alignment or smoothing can also potentially influence allocation by probabilistic cytoarchitectonic maps.

Since the number of studies reporting standard deviations in age-ranges was too small to enable a valid analysis, only the use of mean age-values for correlations was feasible. This surely is a limiting factor for the interpretation of age-related changes, especially since patient and control group were not perfectly matched in all of the (peer-reviewed) papers. The obtained findings may hence be regarded as first evidence for differential findings in VBM studies depending on the age of the assessed patients rather than a comprehensive elucidation of age-related changes or disturbed trajectories in ASD.

In three cases, study populations showed a partial overlap [McAlonan et al., 2005, 2008; Waiter et al., 2004, 2005], and in one case for the high functioning cohort [Salmond et al., 2005, 2007]. Although we regard these overlaps as an important potential limitation of this study, populations obviously were considered disparate enough to constitute for two different peer-reviewed publications in each of the cases. We therefore regard it as reasonable to include them into this meta-analysis and treat them as separate publications in order to quantitatively integrate the current literature on ASD in an unbiased fashion.

Evidently, separate analyses of gray and white matter changes and/or separate analyses of unmodulated (indicating concentration changes) and modulated (indicating volume changes) would be helpful to further corroborate the nature of the observed structural abnormalities in ASD patients. Because of the limited number of available studies, however, these would be grossly underpowered at the moment and were therefore not performed.

Another important limitation is the fact that some but not all studies allow co-medication for their subjects and indeed enrolled ASD patients with medication [Bonhila et al., 2008; Brieber et al., 2007; Waiter et al., 2005]. However, at least for typical antipsychotics have been shown to alter brain structure significantly, resulting especially in basal ganglia volume increases [Scherk and Falkai, 2006]. Thus, our findings, especially concerning the basal ganglia, might in part have been influenced by antipsychotic medication.

In their meta-analysis of volumetric studies on ASD patients, Stanfield and colleagues found evidence for age-related effects on the amygdalae, while both age and IQ were shown to have an impact on the cerebellar vermal lobules VI and VII [Stanfield et al., 2008]. Studies included in this meta-analysis encompassed population with mean IQ ranging from 55.8 to 113.2, while not every study reported mean IQ values. Because of the small number of studies fitting our inclusion criteria, an analysis of IQ-related changes in brain structure was not possible. Thus, a further investigation of IQ effects on brain structure changes in ASD patients seems to be a worthwhile goal for future studies.

Additionally, we were only able to analyze whether there was brain overgrowth or brain atrophy in a certain focus during a given age range. This means that these results can only give a raw perspective on brain growth trajectories. We hope that our study might inspire more longitudinal studies with larger and better clinically better defined samples in this field of research.

Outlook

Acknowledging the caveats listed above, our study provides the first quantitative summary of brain structure changes reported in literature on autism spectrum disorders. In contrast to the rather small sample sizes of the original studies, our meta-analysis encompasses data of 277 ASD patients and 303 healthy controls. This unbiased summary not only provided evidence for consistent structural abnormalities in spite of heterogeneous diagnostic criteria and VBM methodology, but also hinted at a dependency of VBM findings on the age of the included patients as suggested by several longitudinal studies.

A better characterization of subsamples based on their diagnosis and in particular the applied diagnostic tools appears as an important direction for further research. While we here showed convergence of reported VBM findings in multiple regions, the relatively small number of studies contributing to each cluster precludes definitive statements of shared and disjointed morphological changes between diagnostic groups. A larger body of studies with well-defined patient samples, however, should help to elucidate basic pathophysiological mechanisms of autism spectrum disorders. Combined with a better characterization of the cellular mechanisms underlying these macromorphological abnormalities, a more comprehensive understanding of these disorders with the perspective of finding causal treatments might emerge in the long run.

ACKNOWLEDGMENTS

The authors thank Prof. Katrin Amunts (Institute of Neuroscience and Medicine-1, Forschungszentrum Jülich GmbH, Juelich, Germany) for her advice and her support of this study.

REFERENCES

Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, Happé F, Frith C, Frith U (1999): The neuroanatomy of autism: A voxel-based whole brain analysis of structural scans. Neuroreport 10:1647–1651.

Alexander GE, DeLong MR, Strick PL (1986): Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381.

Amaral DG, Schumann CM, Nordahl CW (2008): Neuroanatomy of autism. Trends Neurosci 31:137–145.

Amunts K, Zilles K (2001): Advances in cytoarchitectonic mapping of the human cerebral cortex. Neuroimaging Clin N Am 11:151–169.

Amunts K, Schleicher A, Bürgel U, Mohlberg H, Uylings HB, Zilles K (1999): Broca's region revisited: Cytoarchitecture and intersubject variability. J Comp Neurol 412:319–341.

Amunts K, Malikovic A, Mohlberg H, Schormann T, Zilles K (2000): Brodmann's areas 17 and 18 brought into stereotaxic space-where and how variable? Neuroimage 11:66–84.

Ashburner J, Friston KJ (2000): Voxel-based morphometry—The methods. Neuroimage 11:805–821.

Ashburner J, Friston KJ (2005): Unified segmentation. Neuroimage 26:839–851.

Atmaca M, Yildirim H, Ozdemir H, Tezcan E, Poyraz AK (2007): Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 31:46–52.

Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, Williams SC (1999): Social intelligence in the normal and autistic brain: An fMRI study. Eur J Neurosci 11:1891–1898.

Bartholomeusz HH, Courchesne E, Karns CM (2002): Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults. Neuropediatrics 33:239–241.

Bernabei P, Fenton G, Fabrizi A, Camaioni L, Perucchini P (2003): Profiles of sensorimotor development in children with autism and with developmental delay. Percept Mot Skills 96: 1107–1116.

Bertone A, Mottron L, Jelenic P, Faubert J (2003): Motion perception in autism: a "complex" issue. J Cogn Neurosci 15:218–225.

Blake R, Turner LM, Smoski MJ, Pozdol SL, Stone WL (2003): Visual recognition of biological motion is impaired in children with autism. Psychol Sci 14:151–157.

Bloss CS, Courchesne E (2007): MRI neuroanatomy in young girls with autism: A preliminary study. J Am Acad Child Adolesc Psychiatry 46:515–523.

Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet MH, Barthélémy C, Mouren MC, Artiges E, Samson Y, Brunelle F, Frackowiak RS, Zilbovicius M (2004): Superior temporal sulcus anatomical abnormalities in childhood autism: A voxel-based morphometry MRI study. Neuroimage 23:364–369.

Bonilha L, Cendes F, Rorden C, Eckert M, Dalgalarrondo P, Li LM, Steiner CE (2008): Gray and white matter imbalance—Typical structural abnormality underlying classic autism? Brain Dev 30:396–401.

Brambilla P, Hardan A, di Nemi SU, Perez J, Soares JC, Barale F (2003): Brain anatomy and development in autism: Review of structural MRI studies. Brain Res Bull 61:557–569.

Brieber S, Neufang S, Bruning N, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Fink GR, Konrad K (2007): Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. J Child Psychol Psychiatry 48:1251–1258.

Bürgel U, Schormann T, Schleicher A, Zilles K (1999): Mapping of histologically identified long fiber tracts in human cerebral hemispheres to the MRI volume of a reference brain: Position and spatial variability of the optic radiation. Neuroimage 10:489–499.

Bürgel U, Amunts K, Hoemke L, Mohlberg H, Gilsbach JM, Zilles K (2006): White matter fiber tracts of the human brain: Three-dimensional mapping at microscopic resolution, topography and intersubject variability. Neuroimage 29:1092–1105.

Caron MJ, Mottron L, Rainville C, Chouinard S (2004): Do high functioning persons with autism present superior spatial abilities? Neuropsychologia 42:467–481.

Carper RA, Courchesne E (2005): Localized enlargement of the frontal cortex in early autism. Biol Psychiatry 57:126–133.

Carper RA, Moses P, Tigue ZD, Courchesne E (2002): Cerebral lobes in autism: Early hyperplasia and abnormal age effects. Neuroimage 16:1038–1051.

Caselli RJ (1993): Ventrolateral and dorsomedial somatosensory association cortex damage produces distinct somesthetic syndromes in humans. Neurology 43:762–771.

Caspers S, Geyer S, Schleicher A, Mohlberg H, Amunts K, Zilles K (2006): The human inferior parietal cortex: Cytoarchitectonic parcellation and interindividual variability. Neuroimage 33:430–448.

Caspers S, Eickhoff SB, Geyer S, Scheperjans F, Mohlberg H, Zilles K, Amunts K (2008): The human inferior parietal lobule in stereotaxic space. Brain Struct Funct 212:481–495.

Choi HJ, Zilles K, Mohlberg H, Schleicher A, Fink GR, Armstrong E, Amunts K (2006): Cytoarchitectonic identification and probabilistic mapping of two distinct areas within the anterior ventral bank of the human intraparietal sulcus. J Comp Neurol 495:53–69.

Coon H (2006): Current perspectives on the genetic analysis of autism. Am J Med Genet C Semin Med Genet 142:24–32.

Coskun MA, Varghese L, Reddoch S, Castillo EM, Pearson DA, Loveland KA, Papanicolaou AC, Sheth BR (2009): How somatic cortical maps differ in autistic and typical brains. Neuroreport 20:175–179.

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY (2001): Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. Neurology 57:245–254.

Courchesne E, Carper R, Akshoomoff N (2003): Evidence of brain overgrowth in the first year of life in autism. JAMA 290:337–344.

Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, Morgan J (2007): Mapping early brain development in autism. Neuron 56:399–413.

Craig MC, Zaman SH, Daly EM, Cutter WJ, Robertson DM, Hallahan B, Toal F, Reed S, Ambikapathy A, Brammer M, Murphy CM, Murphy DG (2007): Women with autistic-spectrum disorder: Magnetic resonance imaging study of brain anatomy. Br J Psychiatry 191:224–228.

Dakin S, Frith U (2005): Vagaries of visual perception in autism. Neuron 48:497–507.

Dalton KM, Nacewicz BM, Johnstone T, Schaefer HS, Gernsbacher MA, Goldsmith HH, Alexander AL, Davidson RJ (2005): Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci 8:519–526.

Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K (2007): Rate of head growth decelerates and symptoms worsen in the second year of life in autism. Biol Psychiatry 61:458–464.

De Gelder (2006): Towards the neurobiology of emotional body language. Nat Neursci Rev 7:242–249.

Dementieva YA, Vance DD, Donnelly SL, Elston LA, Wolpert CM, Ravan SA, DeLong GR, Abramson RK, Wright HH, Cuccaro ML (2005): Accelerated head growth in early development of individuals with autism. Pediatr Neurol 32:102–108.

DiMartino A, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP (2009): Funcitonal brain correlates of social and nonsocial processes in autism spectrum disorders: An activation likelihood estimation meta-analysis. Biol Psychiatry 65:63–74.

Dissanayake C, Bui QM, Huggins R, Loesch DZ (2006): Growth in stature and head circumference in high-functioning autism and Asperger disorder during the first 3 years of life. Dev Psychopathol 18:381–393.

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K (2005): A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25:1325–1335.

Eickhoff SB, Heim S, Zilles K, Amunts K (2006a): Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. Neuroimage 32:570–582.

Eickhoff SB, Lotze M, Wietek B, Amunts K, Enck P, Zilles K (2006b): Segregation of visceral and somatosensory afferents: An fMRI and cytoarchitectonic mapping study. Neuroimage 31:1004–1014.

Eickhoff SB, Weiss PH, Amunts K, Fink GR, Zilles K (2006c): Identifying human parieto-insular vestibular cortex using fMRI and cytoarchitectonic mapping. Hum Brain Mapp 27:611–621.

Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT (2009): Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 30:2907–2926.

Fornito A, Yücel M, Patti J, Wood SJ, Pantelis C (2009): Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. Schizophr Res 108:104–113.

Gepner B, Mestre D, Masson G, de Schonen S (1995): Postural effects of motion vision in young autistic children. Neuroreport 6:1211–1214.

Geyer S (2004): The microstructural border between the motor and the cognitive domain in the human cerebral cortex. Adv Anat Embryol Cell Biol 174:1–89.

Geyer S, Ledberg A, Schleicher A, Kinomura S, Schormann T, Bürgel U, Klingberg T, Larsson J, Zilles K, Roland PE (1996): Two different areas within the primary motor cortex of man. Nature 382:805–807.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL (1999): Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 2:861–863.

Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore E, Fox PT (2008): Meta-analysis of gray matter anomalies in schizophrenia: Application of anatomic likelihood estimation and network analysis. Biol Psychiatry 64:774–781.

Goebel R, Khorram-Sefat D, Muckli L, Hacker H, Singer W (1998): The constructive nature of vision: Direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. Eur J Neurosci 10:1563–1573.

Grefkes C, Geyer S, Schormann T, Roland P, Zilles K (2001): Human somatosensory area 2: Observer-independent cytoarchitectonic mapping, interindividual variability, and population map. Neuroimage 14:617–631.

Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006): Anatomical differences in the mirror neuron system and social cognition network in autism. Cereb Cortex 16:1276–1282.

Hardan AY, Kilpatrick M, Keshavan MS, Minshew NJ (2003): Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. J Child Neurol 18: 317–324.

Hardan AY, Muddasani S, Vemulapalli M, Keshavan MS, Minshew NJ (2006): An MRI study of increased cortical thickness in autism. Am J Psychiatry 163:1290–1292.

Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, Gilmore J, Piven J (2005): Magnetic resonance imaging and head circumference study of brain size in autism: Birth through age 2 years. Arch Gen Psychiatry 62:1366–1376.

Hazlett HC, Poe MD, Gerig G, Smith RG, Piven J (2006): Cortical gray and white brain tissue volume in adolescents and adults with autism. Biol Psychiatry 59:1–6.

Haznedar MM, Buchsbaum MS, Hazlett EA, LiCalzi EM, Cartwright C, Hollander E (2006): Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. Am J Psychiatry 163:1252–1263.

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness VS Jr (2004): Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol 55:530–540.

Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, Wasserman S, Soorya L, Buchsbaum M (2005): Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biol Psychiatry 58:226–232.

Horwitz B, Rumsey JM, Grady CL, Rapoport SI (1988): The cerebral metabolic landscape in autism. Intercorrelations of regional glucose utilization. Arch Neurol 45:749–755.

Hrdlicka M (2008): Structural neuroimaging in autism. Neuro Endocrinol Lett 29:281–286.

Huttenlocher PR (1984): Synapse elimination and plasticity in developing human cerebral cortex. Am J Ment Defic 88:488–496.

Huttenlocher PR, de Courten C (1987): The development of synapses in striate cortex of man. Hum Neurobiol 6:1–9.

Jolliffe T, Baron-Cohen S (1997): Are people with autism and Asperger syndrome faster than normal on the embedded figures test? J Child Psychol Psychiatry 38:527–534.

Kates WR, Burnette CP, Eliez S, Strunge LA, Kaplan D, Landa R, Reiss AL, Pearlson GD (2004): Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype for autism. Am J Psychiatry 161:539–546.

Ke X, Hong S, Tang T, Zou B, Li H, Hang Y, Zhou Z, Ruan Z, Lu Z, Tao G, Liu Y (2008): Voxel-based morphometry study on brain structure in children with high-functioning autism. Neuroreport 19:921–925.

Kennedy DN, Lange N, Makris N, Bates J, Meyer J, Caviness VS Jr (1998): Gyri of the human neocortex: An MRI-based analysis of volume and variance. Cereb Cortex 8:372–384.

Kwon H, Ow AW, Pedatella KE, Lotspeich LJ, Reiss AL (2004): Voxel-based morphometry elucidates structural neuroanatomy of high-functioning autism and Asperger syndrome. Dev Med Child Neurol 46:760–764.

Lahaie A, Mottron L, Arguin M, Berthiaume C, Jemel B, Saumier D (2006): Face perception in high-functioning autistic adults: Evidence for superior processing of face parts, not for a configural face-processing deficit. Neuropsychology 20:30–41.

Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, Turkeltaub PE, Kochunov P, Fox PT (2005): ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 25:155–164.

Landa RJ (2008): Diagnosis of autism spectrum disorders in the first 3 years of life. Nat Clin Pract Neurol 4:138–147.

Landa RJ, Holman KC, Garrett-Mayer E (2007): Social and communication development in toddlers with early and later diagnosis of autism spectrum disorders. Arch Gen Psychiatry 64:853–864.

Langen M, Durston S, Staal WG, Palmen SJ, van Engeland H (2007): Caudate nucleus is enlarged in high-functioning medication-naive subjects with autism. Biol Psychiatry 62:262–266.

Lauritsen MB, Pedersen CB, Mortensen PB (2005): Effects of familial risk factors and place of birth on the risk of autism: A nationwide register-based study. J Child Psychol Psychiatry 46:963–971.

Lenroot RK, Giedd JN (2006): Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev 30:718–729.

Levitt JG, Blanton RE, Smalley S, Thompson PM, Guthrie D, McCracken JT, Sadoun T, Heinichen L, Toga AW (2003): Cortical sulcal maps in autism. Cereb Cortex 13:728–735.

Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, Pickles A, Rutter M (2000): The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30:205–223.

Lotspeich LJ, Kwon H, Schumann CM, Fryer SL, Goodlin-Jones BL, Buonocore MH, Lammers CR, Amaral DG, Reiss AL (2004): Investigation of neuroanatomical differences between autism and Asperger syndrome. Arch Gen Psychiatry 61:291–298.

Makris N, Meyer JW, Bates JF, Yeterian EH, Kennedy DN, Caviness VS (1999): MRI-based topographic parcellation of human cerebral white matter and nuclei II. Rationale and applications with systematics of cerebral connectivity. Neuroimage 9:1–17.

Malikovic A, Amunts K, Schleicher A, Mohlberg H, Eickhoff SB, Wilms M, Palomero-Gallagher N, Armstrong E, Zilles K (2007): Cytoarchitectonic analysis of the human extrastriate

cortex in the region of V5/MT: A probabilistic, stereotaxic map of area hOc5. Cereb Cortex 17:562–574.

Mandelbaum DE, Stevens M, Rosenberg E, Wiznitzer M, Steinschneider M, Filipek P, Rapin I (2006): Sensorimotor performance in school-age children with autism, developmental language disorder, or low IQ. Dev Med Child Neurol 48:33–39.

McAlonan GM, Daly E, Kumari V, Critchley HD, van Amelsvoort T, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F, Howlin P, Murphy DG (2002): Brain anatomy and sensorimotor gating in Asperger's syndrome. Brain 125:1594–1606.

McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, Yip L, Murphy DG, Chua SE (2005): Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. Brain 128:268–276.

McAlonan GM, Suckling J, Wong N, Cheung V, Lienenkaemper N, Cheung C, Chua SE (2008): Distinct patterns of grey matter abnormality in high-functioning autism and Asperger's syndrome. J Child Psychol Psychiatry 49:1287–1295.

Merigan WH, Maunsell JH (1993): How parallel are the primate visual pathways? Annu Rev Neurosci 16:369–402.

Merigan WH, Byrne CE, Maunsell JH (1991): Does primate motion perception depend on the magnocellular pathway? J Neurosci 11:3422–3429.

Milne E, Swettenham J, Hansen P, Campbell R, Jeffries H, Plaisted K (2002): High motion coherence thresholds in children with autism. J Child Psychol Psychiatry 43:255–263.

Minshew NJ, Williams DL (2007): The new neurobiology of autism: Cortex, connectivity, and neuronal organization. Arch Neurol 64:945–950.

Mishkin M, Ungerleider LG (1982): Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. Behav Brain Res 6:57–77.

Mottron L, Belleville S, Ménard E (1999): Local bias in autistic subjects as evidenced by graphic tasks: Perceptual hierarchization or working memory deficit? J Child Psychol Psychiatry 40:743–755.

Nacewicz BM, Dalton KM, Johnstone T, Long MT, McAuliff EM, Oakes TR, Alexander AL, Davidson RJ (2006): Amygdala volume and nonverbal social impairment in adolescent and adult males with autism. Arch Gen Psychiatry 63: 1417–1428.

Naito E, Ehrsson HH, Geyer S, Zilles K, Roland PE (1999): Illusory arm movements activate cortical motor areas: A positron emission tomography study. J Neurosci 19:6134–6144.

Naito E, Kinomura S, Geyer S, Kawashima R, Roland PE, Zilles K (2000): Fast reaction to different sensory modalities activates common fields in the motor areas, but the anterior cingulate cortex is involved in the speed of reaction. J Neurophysiol 83:1701–1709.

Nordahl CW, Dierker D, Mostafavi I, Schumann CM, Rivera SM, Amaral DG, Van Essen DC (2007): Cortical folding abnormalities in autism revealed by surface-based morphometry. J Neurosci 27:11725–11735.

Palmen SJ, Hulshoff Pol HE, Kemner C, Schnack HG, Durston S, Lahuis BE, Kahn RS, Van Engeland H (2005): Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychol Med 35:561–570.

Palmen SJ, Durston S, Nederveen H, Van Engeland H (2006): No evidence for preferential involvement of medial temporal lobe structures in high-functioning autism. Psychol Med 36: 827–834.

Paus T, Keshavan M, Giedd JN (2008): Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci 9:947–957.

Pellicano E, Gibson L, Maybery M, Durkin K, Badcock DR (2005): Abnormal global processing along the dorsal visual pathway in autism: A possible mechanism for weak visuospatial coherence? Neuropsychologia 43:1044–1053.

Penn HE (2006): Neurobiological correlates of autism: A review of recent research. Child Neuropsychol 12:57–79.

Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO (1994): A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurol 51:874–887.

Pierce K, Müller RA, Ambrose J, Allen G, Courchesne E (2001): Face processing occurs outside the fusiform "face area" in autism: Evidence from functional MRI. Brain 124:2059–2073.

Pierce K, Haist F, Sedaghat F, Courchesne E (2004): The brain response to personally familiar faces in autism: Findings of fusiform activity and beyond. Brain 127:2703–2716.

Plaisted K, Swettenham J, Rees L (1990): Children with autism show local precedence in a divided attention task and global precedence in a selective attention task. Child Psychol Psychiatry 40:733–742.

Posner MI, DiGirolamo GJ (2000): Cognitive neuroscience: Origins and promise. Psychol Bull 126:873–889.

Redcay E, Courchesne E (2005): When is the brain enlarged in autism? A meta-analysis of all brain size reports. Biol Psychiatry 58:1–9.

Richdale AL, Prior MR (1995): The sleep/wake rhythm in children with autism. Eur Child Adolesc Psychiatry 4:175–186.

Rojas DC, Peterson E, Winterrowd E, Reite ML, Rogers SJ, Tregellas JR (2006): Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. BMC Psychiatry 6:56.

Rottschy C, Eickhoff SB, Schleicher A, Mohlberg H, Kujovic M, Zilles K, Amunts K (2007): Ventral visual cortex in humans: Cytoarchitectonic mapping of two extrastriate areas. Hum Brain Mapp 28:1045–1059.

Salmond CH, Ashburner J, Connelly A, Friston KJ, Gadian DG, Vargha-Khadem F (2005): The role of the medial temporal lobe in autistic spectrum disorders. Eur J Neurosci 22:764–772.

Salmond CH, Vargha-Khadem F, Gadian DG, de Haan M, Baldeweg T (2007): Heterogeneity in the patterns of neural abnormality in autistic spectrum disorders: Evidence from ERP and MRI. Cortex 43:686–699.

Scheperjans F, Eickhoff SB, Hömke L, Mohlberg H, Hermann K, Amunts K, Zilles K (2008a): Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. Cereb Cortex 18:2141–2157.

Scheperjans F, Hermann K, Eickhoff SB, Amunts K, Schleicher A, Zilles K (2008b): Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cereb Cortex 18:846–867.

Scherk H, Falkai P (2006): Effects of antipsychotics on brain structure. Curr Opin Psychiatry 19:145–150.

Schmitz N, Rubia K, Daly E, Smith A, Williams S, Murphy DG (2006): Neural correlates of executive function in autistic spectrum disorders. Biol Psychiatry 59:7–16.

Schmitz N, Daly E, Murphy D (2007): Frontal anatomy and reaction time in Autism. Neurosci Lett 412:12–17.

Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH, Lammers CR, Reiss AL, Amaral DG (2004):

The amygdala is enlarged in children but not adolescents with autism: The hippocampus is enlarged at all ages. J Neurosci 24:6392–6401.

Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, Pierce K, Hagler D, Schork N, Lord C, Courchesne E (2010): Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. J Neurosci 30:4419–4427.

Sears LL, Vest C, Mohamed S, Bailey J, Ranson BJ, Piven J (1999): An MRI study of the basal ganglia in autism. Prog Neuropsychopharmacol Biol Psychiatry 23:613–624.

Shah A, Frith U (1983): An islet of ability in autistic children: A research note. J Child Psychol Psychiatry 24:613–620.

Shah A, Frith U (1993): Why do autistic individuals show superior performance on the block design task? J Child Psychol Psychiatry 34:1351–1364.

Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, Maravilla KR, Giedd JN, Munson J, Dawson G, Dager SR (2002): Brain structural abnormalities in young children with autism spectrum disorder. Neurology 59:184–192.

Spencer J, O'Brien J, Riggs K, Braddick O, Atkinson J, Wattam-Bell J (2000): Motion processing in autism: Evidence for a dorsal stream deficiency. Neuroreport 11:2765–2767.

Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM (2008): Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur Psychiatry 23:289–299.

Takarae Y, Luna B, Minshew NJ, Sweeney JA (2008): Patterns of visual sensory and sensorimotor abnormalities in autism vary in relation to history of early language delay. J Int Neuropsychol Soc 14:980–989.

Tisch S, Silberstein P, Limousin-Dowsey P, Jahanshahi M (2004): The basal ganglia: Anatomy, physiology, and pharmacology. Psychiatr Clin North Am 27:757–799.

Toga AW, Thompson PM, Mori S, Amunts K, Zilles K (2006): Towards multimodal atlases of the brain. Nat Rev Neurosci 7:952–966.

Tootell RB, Reppas JB, Dale AM, Look RB, Sereno MI, Malach R, Brady TJ, Rosen BR (1995): Visual motion aftereffect in human cortical area MT revealed by functional magnetic resonance imaging. Nature 375:139–141.

Tuchman RF, Rapin I, Shinnar S (1991): Autistic and dysphasic children. I: Clinical characteristics. Pediatrics 88:1211–1218.

Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA (2002): Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation. Neuroimage 16:765–780.

Turner KC, Frost L, Linsenbardt D, McIlroy JR, Müller RA (2006): Atypically diffuse functional connectivity between caudate nuclei and cerebral cortex in autism. Behav Brain Funct 2:34.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289.

Volkmar FR, Nelson DS (1990): Seizure disorders in autism. J Am Acad Child Adolesc Psychiatry 29:127–129.

Volkmar FR, Pauls D (2003): Autism. Lancet 362:1133–1141.

Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A (2004): A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. Neuroimage 22:619–625.

Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A (2005): Structural white matter deficits in high-functioning individuals with autistic spectrum disorder: A voxel-based investigation. Neuroimage 24:455–461.

Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S (2004): Fiber tract-based atlas of human white matter anatomy. Radiology 230:77–87.

Wang J, Zhou T, Qiu M, Du A, Cai K, Wang Z, Zhou C, Meng M, Zhuo Y, Fan S, Chen L (1999): Relationship between ventral stream for object vision and dorsal stream for spatial vision: An fMRI ERP study. Hum Brain Mapp 8:170–181.

Watson JD, Myers R, Frackowiak RS, Hajnal JV, Woods RP, Mazziotta JC, Shipp S, Zeki S (1993): Area V5 of the human brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. Cereb Cortex 3:79–94.

Whiteside SP, Port JD, Abramowitz JS (2004): A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. Psychiatry Res 132:69–79.

Wilms M, Eickhoff SB, Specht K, Amunts K, Shah NJ, Malikovic A, Fink GR (2005): Human V5/MT: Comparison of functional and cytoarchitectonic data. Anat Embryol (Berl) 210:485–495.

Young JP, Geyer S, Grefkes C, Amunts K, Morosan P, Zilles K, Roland PE (2003): Regional cerebral blood flow correlations of somatosensory areas 3a, 3b, 1, and 2 in humans during rest: A PET and cytoarchitectural study. Hum Brain Mapp 19: 183–196.

Zeegers M, Pol HH, Durston S, Nederveen H, Schnack H, Daalen EV, Dietz C, Engeland HV, Buitelaar J (2008): No differences in MR-based volumetry between 2- and 7-year-old children with autism spectrum disorder and developmental delay. Brain Dev 31:725–730.

Zilles K, Palomero-Gallagher N, Grefkes C, Scheperjans F, Boy C, Amunts K, Schleicher A (2002): Architectonics of the human cerebral cortex and transmitter receptor fingerprints: Reconciling functional neuroanatomy and neurochemistry. Eur Neuropsychopharmacol 12:587–599.