

Original article

Gray and white matter imbalance – Typical structural abnormality underlying classic autism?

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Abstract

Recent evidence supports increased cortical activity and impaired brain connectivity in autism, but the structural correlates of these abnormalities are not yet defined. We performed a voxel based morphometry analysis of brain MRI from patients with autism selected from a group of 103 subjects with pervasive developmental disorders. Twelve male patients with mean age of 12.4 ± 4 years were compared with 16 matched controls. Patients with autism exhibited increase in gray matter in medial and dorsolateral frontal areas, in the lateral and medial parts of the temporal lobes, in the parietal lobes, cerebellum and claustrum. Patients also showed decrease in frontal, parietal, temporal and occipital white matter. The combination of enlarged cortex and reduced white matter is possibly the structural basis of some symptoms of classic autism.

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1. Introduction

Autism is most likely caused by a disruption in the sophisticated cascade of events that take place during brain development. However, the functional and structural consequences of these altered steps are largely unclear. It is also unknown if these abnormalities are consistent across subjects with autism, therefore leading to the symptoms that characterize autism, or if conver-

gent symptoms can arise from different brain abnormalities.

There is remarkably low reliability in reported brain structural abnormalities related to autism, both regarding histological and imaging studies. For example, post-mortem studies have reported abnormal cortical structure associated with autism, but conclusions vary from reduced neuronal cell size and increased cell packing density in areas of the limbic system [1–3], irregular laminar patterns [1] and more numerous cortical minicolumns [4].

Similarly, imaging studies have provided few consistent findings. One of the rare common observations is that the overall brain volume is significantly larger in autistic children [5–7]. Other findings, particularly when

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other age ranges are studied, have proved both difficult to replicate and conflicting. For example, some studies have reported a decreased gray matter in the superior temporal sulcus [8], fronto-striatal and parietal areas [9,10], right paracingulate sulcus and left inferior frontal gyrus [10]. Other studies, in turn, observed increased gray matter in amygdala/peri-amygdaloid cortex, middle temporal gyrus, inferior temporal gyrus [10], fusiform gyrus, inferior cerebellum, dorsolateral prefrontal cortex, peri-hippocampal cortex, and lateral occipito-temporal sulcus [11].

Despite the many inconsistencies, there is a trend from more recent studies to observe regional increase of gray matter [11,12], accompanied with local reduction of white matter [13]. These findings support previously well established remarks about brain enlargement in autism [6], and more recent functional observations regarding increased local but reduced long-distance cortical-cortical reciprocal activity and coupling [7,14].

It is possible that discrepant findings from morphometrical studies arise for two reasons. One cause may be studying different populations of patients within the autistic spectrum who exhibit different patterns of structural abnormalities, even though symptoms are moderately similar. Alternatively, this difference might also arise from different techniques of imaging analysis and small sample sizes.

In this study, we aimed to investigate if there is a reproducible pattern of abnormalities in the brain of patients with autism. We performed a refined voxel based morphometry (VBM) analysis of patients with classic autism carefully selected from 103 patients with pervasive developmental disorder.

2. Methods

Patients with autism were selected from a large cohort composed of 103 patients with pervasive developmental disorder, described in detail elsewhere [15].

The diagnosis of autism was performed by a thorough neurological investigation composed by a comprehensive history, assessment and physical examination. In the present study, we only included those patients who fulfilled the diagnosis for autism as defined by the DSM-IV and ICD-10 criteria (Table 1). All individuals had normal results on screening tests for inborn errors of metabolism, normal (46,XY) chromosomal constitution on lymphocytes analysis (G-banding) and negative FRAXA mutation on Southern blotting analysis. None of them had consanguineous parents. Patients who did not meet all criteria for the diagnosis of autism were excluded. Twelve patients, all male, with mean age of 12.4 ± 4 , fulfilled the diagnostic criteria for classic autism and were included in this study (Table 1).

As a control group, we studied 16 boys, with mean age of 13.2 ± 5 years, without previous medical history. Group differences for age were assessed using a *t*-test. The statistical threshold was set at $p < 0.05$. All legal representatives of the individuals enrolled in this study signed a written consent, approved by the hospital's institutional review board.

We used T1-weighted images with 1 mm isotropic voxels, acquired in a 2T scanner (Elscent Prestige®) using a spoiled gradient-echo sequence (TR = 22 ms, TE = 9 ms, flip angle = 35°, matrix = 256 × 220). Optimized VBM analysis was performed using SPM5 (www.fil.ion.ucl.ac.uk). DICOM images were transformed into ANALYZE format using MRICro [16]. A T1 template in the standard MNI stereotaxic space was created from the images of the control group. Prior maps of gray matter, white matter and CSF were also generated from our sample of controls. The prior images and the template were convolved with an Isotropic Gaussian Kernel (IGK) of 8 mm and were used for optimizing the non-linear normalization. Using a template based on our own population optimizes normalization and tissue segmentation because: (1) it overcomes differences in contrasts from our images to the MNI 152 brain

Table 1
Clinical profile of the patients investigated in this study

Subject	Age	DSM-IV criteria	MR	Medication	EEG
1	14y10m	1a, 1b, 1c, 2d, 3a, 3c, 3d	+	CBZ	Generalized epileptif. activity
2	9y11m	1a, 1b, 1c, 2a, 2c, 2d, 3a, 3b, 3c, 3d	+	–	Epileptif. activity, L temporal
3	11y1m	1a, 1b, 1c, 2d, 3a, 3c, 3d	–	–	Normal
4	5y9m	1a, 1b, 1c, 2a, 2b, 2c, 2d, 3a, 3b, 3d	–	–	Epileptif. activity, L centro-temporal
5	13y	1a, 1b, 1c, 2a, 2d, 3a, 3b, 3c	+	–	Normal
6	10y11m	1a, 1c, 2a, 2d, 3, 3b, 3c, 3d	–	Haloperidol	Normal
7	23y4m	1a, 1b, 1c, 2a, 2b, 2c, 2d, 3a, 3b, 3c, 3d	–	Haloperidol, thioridazine, imipramine	Normal
8	13y8m	1a, 1b, 1c, 2a, 2d, 3a, 3b, 3c, 3d	+	–	Normal
9	9y2m	1a, 1b, 1c, 2a, 3a, 3c	+	–	Normal
10	8y1m	1a, 1b, 2a, 2d, 3b, 3c	+	–	Normal
11	13y	1b, 1d, 2b, 2c, 3c, 3d	–	CBZ, haloperidol	Normal
12	15y10m	1a, 1b, 1c, 2a, 2b, 2c, 2d, 3a	–	Thioridazine, pyridoxine	Normal

Key: MR, mental retardation; +, present; –, absent; CBZ, carbamazepine; L, left.

Table 2
Areas of increased gray matter volume in subjects with autism compared with controls

	<i>x, y, z (mm)</i>	<i>T</i>	<i>Z</i>	<i>p(FDR)</i>
<i>Left hemisphere</i>				
Inferior frontal gyrus (BA 47)	−17, 29, −12	6.25	4.84	0.024
Cuneus (BA 30)	−29, −75, 5	6.06	4.74	0.024
Cingulate gyrus (BA 31)	−17, −49, 21	5.82	4.62	0.024
Clastrum	−25, −11, 17	5.72	4.56	0.024
Precuneus (BA 7)	21, −49, 43	5.72	4.56	0.024
Middle temporal gyrus (BA 20)	−56, −34, −7	5.67	4.53	0.024
Middle temporal gyrus (BA 19)	−37, −77, 19	5.58	4.49	0.024
Thalamus (pulvinar)	−5, −29, 17	5.53	4.45	0.024
Superior frontal gyrus	−14, 51, 28	5.49	4.43	0.024
Cingulate gyrus (BA 32)	−17, 6, 41	5.47	4.42	0.024
Superior parietal lobule (BA 7)	−25, −51, 43	5.47	4.42	0.024
Inferior temporal gyrus (BA 20)	−47, −26, −12	5.41	4.39	0.024
Insula (BA 13)	−41, −42, 24	5.36	4.36	0.024
Putamen	−20, −5, 13	5.36	4.36	0.024
Superior temporal gyrus (BA 22)	50, −7, −4	5.32	4.34	0.024
Anterior cingulate (BA 32)	16, 30, −9	4.98	4.14	0.024
Fusiform gyrus (BA 19)	37, −73, −12	4.97	4.13	0.024
Superior frontal gyrus (BA 8)	−11, 36, 45	4.94	4.11	0.024
Middle occipital gyrus (BA 18)	−20, −91, 8	4.93	4.11	0.024
Cuneus (BA 18)	−18, −87, 21	4.87	4.07	0.024
Lingual gyrus	−23, −79, 3	4.83	4.04	0.024
Precentral gyrus (BA 6)	−37, −8, 26	4.71	3.97	0.025
Superior temporal gyrus (BA 39)	−39, −52, 32	4.71	3.97	0.025
Middle temporal gyrus (BA 37)	50, −55, −2	4.69	3.96	0.025
Postcentral gyrus (BA 5)	−25, −44, 61	4.67	3.94	0.025
Cerebellum (declive)	36, −83, −18	4.6	3.9	0.025
Inferior occipital gyrus (BA 18)	−33, −84, −9	4.58	3.89	0.025
Cerebellum (pyramis)	30, −76, −31	4.46	3.81	0.026
Inferior frontal gyrus (BA 46)	33, 31, 10	4.45	3.8	0.026
Superior frontal gyrus (BA 10)	−16, 59, 9	4.42	3.78	0.026
Cingulate gyrus (BA 24)	−15, −2, 47	4.41	3.78	0.026
Superior frontal gyrus (BA 6)	−15, 9, 58	4.38	3.76	0.026
Middle temporal gyrus (BA 39)	−38, −53, 5	4.36	3.74	0.026
Thalamus	−27, −28, 6	4.34	3.73	0.027
Fusiform gyrus (BA 37)	48, −41, −14	4.33	3.73	0.027
Parahippocampal gyrus (BA 19)	17, −46, −3	4.3	3.7	0.027
Medial frontal gyrus (BA 11)	5, 37, −15	4.28	3.69	0.027
Inferior frontal gyrus (BA 45)	−45, 33, 4	4.27	3.68	0.027
Medial frontal gyrus (BA 9)	−19, 34, 28	4.27	3.69	0.027
<i>Right hemisphere</i>				
Superior frontal gyrus (BA 8)	10, 36, 44	5.98	4.7	0.024
Inferior occipital gyrus (BA 18)	23, −90, −7	5.86	4.63	0.024
Precuneus (BA 7)	21, −49, 43	5.72	4.56	0.024
Cingulate gyrus (BA 24)	23, −19, 39	5.34	4.35	0.024
Superior temporal gyrus (BA 22)	50, −7, −4	5.32	4.34	0.024
Superior frontal gyrus (BA 10)	19, 56, −7	5.27	4.31	0.024
Cingulate gyrus (BA 31)	16, −48, 21	5.2	4.27	0.024
Posterior cingulate (BA 23)	4, −27, 19	5.01	4.15	0.024
Anterior cingulate (BA 32)	16, 30, −9	4.98	4.14	0.024
Fusiform gyrus (BA 19)	37, −73, −12	4.97	4.13	0.024
Superior parietal lobule (BA 7)	17, −53, 58	4.87	4.07	0.024
Superior frontal gyrus (BA 6)	20, 8, 56	4.86	4.06	0.024
Medial frontal gyrus (BA 10)	18, 50, 6	4.84	4.05	0.024
Thalamus (pulvinar)	26, −28, 6	4.81	4.03	0.024
Cuneus (BA 18)	16, −80, 17	4.75	4	0.025
Middle temporal gyrus (BA 37)	50, −55, −2	4.69	3.96	0.025
Cerebellum (declive)	36, −83, −18	4.6	3.9	0.025
Thalamus	24, −21, 14	4.52	3.85	0.025
Cerebellum (pyramis)	30, −76, −31	4.46	3.81	0.026
Inferior frontal gyrus (BA 46)	33, 31, 10	4.45	3.8	0.026

Table 2 (continued)

	<i>x, y, z (mm)</i>	<i>T</i>	<i>Z</i>	<i>p(FDR)</i>
Insula (BA 13)	32, -7, 20	4.39	3.76	0.026
Middle frontal gyrus (BA 6)	20, 1, 60	4.36	3.74	0.026
Superior temporal gyrus (BA 39)	41, -49, 25	4.34	3.73	0.027
Fusiform gyrus (BA 37)	48, -41, -14	4.33	3.73	0.027
Parahippocampal gyrus (BA 19)	17, -46, -3	4.3	3.7	0.027
Medial frontal gyrus (BA 11)	5, 37, -15	4.28	3.69	0.027
Caudate	39, -24, -7	4.25	3.67	0.027
Middle temporal gyrus (BA 39)	43, -70, 16	4.22	3.65	0.027
Medial frontal gyrus (BA 9)	16, 45, 17	4.16	3.61	0.028
Inferior parietal lobule (BA 7)	36, -59, 44	4.07	3.54	0.029

Table 3

Areas of reduced white matter volume in subjects with autism

	<i>x, y, z (mm)</i>	<i>T</i>	<i>Z</i>	<i>p(FDR)</i>
<i>Left hemisphere</i>				
Cuneus	-46, -13, -21	6.32	4.87	0.02
Middle temporal gyrus	10, 37, 44	6.22	4.83	0.02
Sub-gyral	12, 28, 45	6.02	4.72	0.02
Inferior frontal gyrus	-39, 39, -11	5.93	4.67	0.02
Middle frontal gyrus	-58, -53, 25	5.72	4.56	0.02
Supramarginal gyrus	17, 5, 50	5.3	4.33	0.02
Parahippocampal gyrus	17, 37, -19	4.82	4.04	0.02
Uncus	-23, -15, -36	4.45	3.8	0.021
Postcentral gyrus	33, 32, 9	4.41	3.77	0.021
Cerebellar tonsil	53, -17, 18	4.3	3.7	0.022
Superior frontal gyrus	23, -7, -33	4.14	3.59	0.023
Precentral gyrus	-22, -9, 71	3.99	3.49	0.025
Cingulate gyrus	-35, -9, 47	3.82	3.38	0.027
Superior temporal gyrus	-2, 63, 2	3.53	3.16	0.031
Medial frontal gyrus	12, 59, -24	3.49	3.13	0.032
Precuneus	18, 32, -30	3.28	2.97	0.038
Anterior cingulate	60, -45, 12	3.21	2.92	0.04
Thalamus	-7, 57, -15	3.06	2.8	0.045
Insula	19, 28, -28	2.97	2.73	0.048
Fusiform gyrus	48, -37, 25	2.93	2.7	0.049
<i>Right hemisphere</i>				
Superior temporal gyrus	59, -18, -5	7.28	5.33	0.02
Superior frontal gyrus	12, 36, 55	6.07	4.75	0.02
Middle frontal gyrus	14, -1, 66	5.19	4.26	0.02
Superior parietal lobule	37, -54, 3	5.18	4.26	0.02
Cuneus	44, -70, 16	5.02	4.16	0.02
Inferior temporal gyrus	32, -75, 4	4.84	4.05	0.02
Anterior cingulate	8, 26, -8	4.68	3.95	0.02
Medial frontal gyrus	-17, 30, -12	4.4	3.77	0.021
Postcentral gyrus	51, -57, -2	4.36	3.74	0.022
Middle temporal gyrus	-57, -34, -7	4.35	3.73	0.022
Cerebellar tonsil	-21, -35, -39	4.31	3.71	0.022
Uncus	-16, -27, 69	4.13	3.59	0.023
Inferior frontal gyrus	18, 50, 6	3.9	3.43	0.026
Parahippocampal gyrus	42, 2, -35	3.9	3.43	0.026
Insula	64, 24, 0	3.57	3.19	0.031
Posterior cingulate	-52, 0, -8	3.46	3.11	0.033
Inferior semi-lunar lobule	-46, 17, 50	3.38	3.05	0.035
Precuneus	4, 61, -10	3.32	3.01	0.036
Precentral gyrus	-14, -63, 43	3.31	2.99	0.037
Orbital gyrus	-37, 5, 46	3.24	2.94	0.038
Inferior parietal lobule	-4, 9, 21	3.23	2.93	0.039
Cingulate gyrus	-73, -8, 26	3.04	2.78	0.045
Culmen	26, 37, 48	3	2.76	0.047

template, (2) it takes into account non-uniformities in image intensity and inhomogeneities in B0 field created by our scanner and (3) it encompasses differences in the demographics of our population compared to the population of the MNI 152 brain template.

Spatially normalized images were “modulated” in order to preserve the total amount of signal in the images [17], therefore, areas that are expanded during warping are correspondingly reduced in intensity. Spatially normalized images were then re-sliced to an isotropic 1 mm. Images underwent segmentation of gray and white matter using SPM5, estimating the probability of each voxel being gray or white matter. Images were smoothed with an isotropic gaussian kernel of 10 mm to minimize inter-individual gyral variability.

Normalized, segmented and smoothed images were submitted to voxel-wise statistical comparison. We investigated differences in gray and white matter volume between patients with autism and controls. Contrasts were defined in order to estimate the probability of each voxel being gray matter. This analysis included proportional threshold masking (set to 0.8) and implicit masking. Voxel-wise analyses were corrected for multiple comparisons through false discovery rate threshold of 5%.

3. Results

We evaluated 12 subjects with classic autism. There was no significant difference in the mean age ($t(26) = 0.6$, $p = 0.5$) between the 16 controls and patients.

The results from the analysis are given in a parametric map of t -statistic (SPM(t)), and the SPM(t) is corrected for normal distribution (SPM(z)). There was a significant increase in regional gray matter and decrease in regional white matter in subjects with autism.

Increased gray matter in patients with autism was typically bilateral and encompassed the cingulate gyrus, caudate, cerebellum, claustrum, cuneus, fusiform gyrus, inferior, middle and superior frontal gyri, infe-

rior and superior temporal gyri, inferior and superior parietal lobules, pre and post-central gyrus, precuneus, putamen, thalamus, insula and occipital cortex. The local maxima and spatial coordinates of differences in gray matter are outlined in Table 2 and illustrated in Fig. 1.

Decreased white matter was also observed to be mostly bilateral, in or underlying the cuneus, medial and superior frontal gyri, pre- and post-central gyri, inferior parietal lobule, supramarginal gyrus, cingulate gyrus, middle occipital gyrus, parahippocampal gyrus, and the middle and superior temporal gyri. Results from the white matter analyses are summarized in Table 3 and Fig. 1.

We did not observe areas of reduced gray matter or excessive white matter in autism.

4. Discussion

The incidence and prevalence of autism have consistently increased over the past few decades [18,19]. It is not clear if this is related to a true increase in frequency of the disorder, or to an increase in awareness, leading to more diagnosed cases. Regardless of the cause, the high incidence of autism greatly contrasts with the incomplete knowledge of its neurobiology.

In this manuscript, we provide evidence that adolescents and young adults with autism exhibit structural brain abnormalities defined by larger volume of gray matter and reduced volume of white matter. These results are in agreement with recent evidence that suggests that patients with autism have increased cortical cell density [2,3,20], abnormal brain growth particularly during the first few years of life [6,21], abnormally increased regional gray matter in children with autism [11] and reduced white matter underlying most of abnormal cortical regions in children and teenagers with autism [9,13]. Moreover, these results corroborate current findings that indicate autism is associated with increased local cortical activity but reduced long-distance connectivity [7,14].

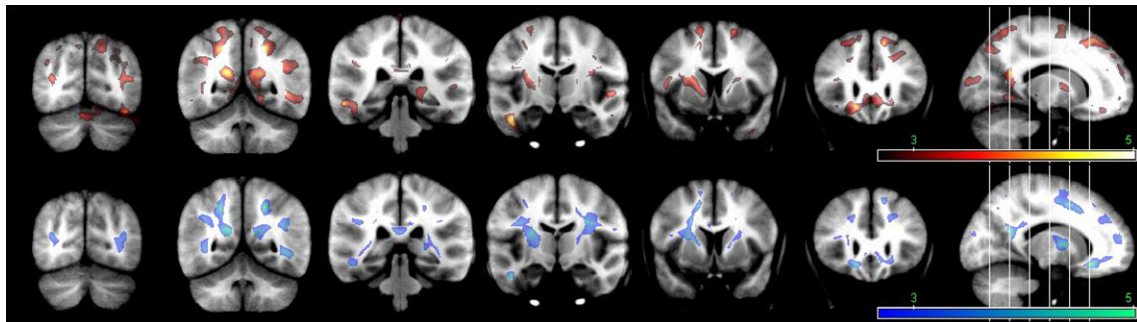


Fig. 1. Top row shows areas of increased gray matter volume (in ‘hot’), while the bottom row shows areas of reduced white matter volume (in ‘cold’) in subjects with a autism compared to healthy controls. Results are overlaid on a mean image of the brain from all control subjects studied, in neurological convention, i.e., the right side of the images corresponds to the right side of the brain. The scale bars indicate Z scores.

Some factors might explain why the present findings are concordant only with more recent VBM studies, and likewise why findings from previous studies have been isolated and not frequently replicated. The autistic spectrum disorder encompasses a broad range of severity of symptoms. In effect, the diagnostic criteria for an autistic-spectrum disorder are fulfilled by any subject with impaired social skills, whose acquisition of language occurred late and who lacks cognitive flexibility [22]. In this manuscript, we studied a group of patients selected based on a range of common symptoms from a large cohort of patients with autistic-spectrum disorder. The homogeneity of our sample, compared to a demographically matched population could have contributed to increased power to detect significant effects. Moreover, the presence of confounding factors, for example seizures and the use of antiepileptic medications, can explain why some reports observed decreased cerebellar volumes and others reported cerebellar hyperplasia [23].

Methodological differences between previous VBM studies can also explain some of the discrepancy in earlier findings. Salmond et al. [11] observed that previous VBM studies have used only linear spatial normalization [10] or have not reported results thresholded after correction for multiple comparisons [9,10,24]. When newer forms of morphometry or VBM optimized for tissue classification have been used, increased regional gray matter concentration has been consistently reported [11,25].

In summary, our VBM findings suggest that cortical regions in patients with autism are enlarged and probably abnormally structured. Our findings also indicate that autism is associated with reduced white matter, which is a possible substrate for impaired connectivity between brain areas. The combination of abnormally structured cortex, with impaired connectivity between these brain sites, can help explain some of the behavioral symptoms of classic autism.

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