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Structural MRI-based brain morphology study in infants and toddlers with Down syndrome; the effect of comorbidities

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Abstract

OBJECTIVE: Down syndrome (DS) is the most prevalent chromosomal disorder characterized by intellectual disability, multiple organ anomalies, generalized muscular hypotonia, and characteristic physical features. The presence of congenital cardiac disease, infantile spasms, and congenital hypothyroidism that are often observed in DS patients have contributed to brain morphologic changes. The aim of this study was to evaluate brain morphologic characteristics during infant and toddler ages in patients with DS using structural brain magnetic resonance images (MRI).

METHODS: Structural brain T1-weighted MRI from DS participants with complete chromosome 21 trisomy (n=20; 1.6 ± 0.6 [mean±standard deviation] years old) were analyzed with FreeSurfer. The measurements were compared to those of 60 gender- and age-matched neurotypical controls with Cohen's *d* statistic and unpaired *t*-test with the false discovery rate correction for multiple comparisons, and analyzed by univariate general linear model with the following DS-associated medical comorbidities: congenital cardiac disease, infantile spasms, and hypothyroidism.

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Author Contributions

T.S. was responsible for study design. T.S., J.L and E.T. analyzed data, and T.S., J.L., N.B., and E.T. wrote/edited the manuscript.

Conflict of Interest

T.S., J. L., N.B. and E. T. declare relevant no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

RESULTS: We identified 27 candidate measurements with large effect sizes (absolute d >0.8) and statistically significant differences ($p < 6.9 \times 10–3$). Among them, decreased volumes in bilateral cerebellar gray matter (GM), right cerebellar white matter, brainstem, and cortical abnormalities in the right superior temporal, right rostral anterior cingulate, and left rostral middle frontal gyrus, independent of comorbid effects. Only bilateral cerebellar GM volumes and brainstem volume showed differences between DS and healthy groups during infancy.

CONCLUSION: These results suggest that cerebellar GM and brainstem may represent the primary regions affected by the presence of an additional copy of chromosome 21.

Keywords

brain morphology; cerebellum; brainstem; epilepsy; hypothyroidism

1. INTRODUCTION

Down syndrome (DS, OMIM 190685), or trisomy 21, is the most prevalent chromosomal disorder with an incident rate of over 1 per 700 live births.[1] DS is characterized by intellectual disability, multiple organ anomalies, generalized muscular hypotonia, and characteristic physical features such as a flat nasal bridge, upward-slanting palpable fissure, and single transverse palmar crease.[2] Cognitive impairment in DS is characterized by learning, memory, and speech/language problems.[1] Other major medical comorbidities include congenital cardiac disease (40–50%), hearing loss (75%), eye disease (60%), thyroid disease (4–18%), and seizures (1–13%) such as infantile spasms.[2] Prior neuropathological studies revealed several abnormalities in brain development in DS such as neuronal migration, a hypocellular hippocampal dentate gyrus, and reduced cerebellar expansion during the late prenatal period.[3] In the cerebral cortex of fetal DS brains, delayed and disorganized cortical lamination[4] and low concentration of neurotransmitters[5] have been reported.

Neuroimaging has the potential to play an important role in further understanding neurological and neurodevelopmental impairments in DS. Although at least 14 structural brain magnetic resonance imaging (MRI) studies have been published so far, the majority of them focused on DS patients greater than 5 years old (YO).[1] The presence of congenital cardiac disease,[6] infantile spasms,[7] and congenital hypothyroidism[8] that are often observed in DS patients have contributed to brain morphologic changes in prior structural brain MRI studies with non-DS patients. Infants with congenital cardiac diseases had smaller brain measures in the frontal lobe, parietal lobe, cerebellum, and brainstem.[6] Infants with infantile spasms had various developmental or acquired structural abnormalities in 71% of cases according to a quantitative study.[7] Children with congenital hypothyroidism had regional thickening or thinning in cortical thicknesses.[8]

Moreover, DS patients show accelerated ageing both in clinical symptoms and structural brain MRI in adult ages.[9] Because infantile spasms occur in late infancy[2,7] and the risk of hypothyroidism increases with age,[2] brain morphology in DS is expected to be affected by comorbidities and aging. Therefore, analysis of young children with DS that considers the effects of comorbidities may assist in accurately revealing abnormal brain morphology

associated with DS. In this study, we explored brain morphology in DS patients under 3 YO, through a comparative analysis with neurotypical controls (NC) while considering the effects of comorbidities.

2. METHODS

2.1. Participants

After approval by the Institutional Review Board at Boston Children Hospital (BCH), we reviewed electronic medical records from June 1st, 2008 to February 24th, 2016, to assemble a cohort of patients with DS. Gender- and age-matched NC were selected from our in-house database composed of electronic records of healthy participants without neurological disorders, neuropsychological disorders or epilepsy.[10] After excluding 3 DS cases (see below), we used data from 20 patients with DS (13 males and 7 females) and 60 NC participants (39 males and 21 females). The leading reasons for the MRI examination in neurotypical controls were headaches (60%), to rule out intracranial pathologies (13%), vomiting (11%), and night awakenings (10%). The indications for MRI scans in the DS group were the assessments of various diseases such as nystagmus, papilledema, spasmus nutans, and infantile spasms.

2.2. Structural MRI acquisition and processing

Both DS and NC participants ware imaged with the same model of clinical 3T MRI scanners (Skyra, Siemens Medical Systems, Erlangen, Germany) at BCH. Because of the clinical and retrospective nature of this study, there is variability in the pulse sequences employed to acquire T1-weighted volumetric examinations. Spatial resolution varied in the x and y directions from 0.219 to 1.354 mm (mean: 0.917 mm, standard deviation [SD]: 0.124 mm). Through-plane slice thickness varied from 0.500 to 2.000 mm (mean: 0.996 mm, SD: 0.197 mm). After excluding low quality images due to motion artifacts, DICOM files of T1-weighted volumetric examinations were accessed through the Children's Research and Integration System[11] and analyzed with the recon-all command on FreeSurfer version 5.3.[12] Through this process, 1,573 regionally distributed measurements (463 for regional volume, 448 for surface area, and 662 for cortical thickness) were extracted from each imaging examination. The measurements were extracted using the brain atlases ("aseg.stats") for subcortical segmentation and ("aparc", "aparc.a2009s", and "aparc.DKT40") for automatic cortical paracellations.

Each FreeSurfer output from a T1 structural examination displayed with a labeled overlay map on FreeView (https://surfer.nmr.mgh.harvard.edu) were visually inspected for quality of regional segmentation results, and examinations were excluded from analysis despite manual corrections if FreeSurfer results were observed to substantially fail. Three scans of 3 DS cases were excluded from this study because of such failed FreeSurfer processing. After excluding these cases, there were 20 structural brain MR examinations from 20 DS participants. Age at MRI scans were not significantly different ($T(78) = -0.096$, $p = 0.92$) between DS and NC on a Student's t test (1.6 ± 0.6 and 1.6 ± 0.5 [mean ± SD] in both DS and NC, respectively).

2.3. Statistical analysis

The equality of means in each brain morphology measurement between DS and NC participants were evaluated with Cohen's *d* test, Levene's test for equality of variances, and a two-tailed unpaired *t* test for two groups of samples with the false discovery rate correction (q=0.005) for multiple comparisons. We identified candidate measurements with large size effects (absolute d > 0.8) and statistically significant differences ($p < 6.9 \times 10^{-3}$). For each identified measurement, a Univariate General Linear Model (GLM) ($p < 0.05$) was constructed to evaluate the effects of binary or continuous covariates (age, gender, and presence of congenital cardiac disease, infantile spasms, and hypothyroidism). Critical values from the F-distribution calculation were determined to be F(0.05,6,73) = 2.22 and F(0.05, 1,73) = 3.97 for the corrected model and each covariate, respectively. Statistical analysis was performed using IBM SPSS Statistics version 19 (IBM Corp. Armonk, NY).

3. RESULTS

DS participants in the current study showed complete 21 trisomy in all cases, congenital cardiac disease in 75% (atrioventricular canal defect in 35%, ventricular septal defect in 15%, and others in 25%), infantile spasms in 15%, and hypothyroidism in 30% (Table 1). The total volumes of the intra-cranial space, cortical gray matter (GM), cortical white matter (WM), and subcortical GM were not statistically significantly different in DS and NC participants (Table 2).

Among measurements generated by the FreeSurfer recon-all pipeline, 19 brain morphologic measurements were identified for further analyses as the candidate measurements with large effect sizes and statistically significant *p* values (Table 3). The 19 candidate measurements included cerebellar volumes, brainstem volume, and some cortical measurements (surface areas, volumes, and SD of the thickness) (Table 3).

Univariate GLM demonstrated that the presence of DS was an independent significant factor in the differences observed in bilateral cerebellar GM volumes, right cerebellar WM volume, brainstem volume, volume and surface area of the right rostral anterior cingulate cortex (ACC), volume of the right superior temporal cortex (STC), and SD of the cortical thickness of the left rostral middle frontal cortex (MFC). For these identified measurements, age was always a statistically significant covariate. The comparison between DS and NC was statistically significantly affected by gender, while not by any presence of comorbidities (congenital cardiac disease, infantile spasms, and hypothyroidism) (Table 4). Bilateral cerebellar GM volumes and brainstem volumes have demonstrated marked disparity in the infantile period between DS and NC participants (Fig. 1A,B,D). In the right cerebellar WM volume, and right STC volume, and right rostral ACC volume, a gradually increasing difference between the two groups was observed as age increased after about 2 YO (Fig. 1C,E,F).

4. DISCUSSION

We quantitatively evaluated brain morphology in infants and toddlers with DS using structural MRI. Our results showed decreased volumes in the bilateral cerebellar GM, right

cerebellar WM, and brainstem, as well as cortical abnormalities in the right STC, right rostral ACC, and left rostral MFC in DS patients. While the timing of the comorbidities was different such as CHD in early infancy, IS in late infancy, and hypothyroidism at any age, our analysis indicates that these differences in brain morphology develop over time. Only bilateral cerebellar GM volumes as well as the brainstem volume were observed as statistically significantly different between our two groups in infancy.

Prior brain morphologic studies in children with DS[13–20] demonstrated decreased volumes in the global cerebrum,[15,16,20] cerebellum,[13,18–20] and brainstem.[13,14,19] In contrast to findings of global brain volume loss, regionally preserved volumes in the temporal GM[19] and WM[20], parietal GM[20] and WM[19], and subcortical GM[20] were reported.

Only two studies reported brain morphology of infants and toddlers with DS, to the best of our knowledge.[13,14] Gunbey et al (2017) analyzed structural brain MRI of 10 DS patients with the mean age of 2.6 YO, and reported decreased volume in the brainstem, thalamus, basal ganglia, cerebellar cortex, right cerebellar WM, and corpus callosum.[13] An additional analysis assessed brainstem components in 32 DS patients with a mean age of 3.7 YO, and they noted a smaller pons in DS compared to NC.[14] Similarly, the pontine hypoplasia has been noted in adults with DS.[21] The findings of decreased volume in the cerebellar cortex and brainstem are consistent with our results. The “brainstem” in the FreeSurfer version 5.3 pipeline includes the medulla oblongata, the pons, the midbrain, and the superior cerebellar peduncle. However, the volumes of the substructures of “brainstem” are not generated by the recon-all command with FreeSurfer version 5.3. Therefore, we could not reconfirm the pontine hypoplasia in DS. It is possible that the pontine hypoplasia often observed in DS is the leading abnormality of our findings.

The measurements in our study using FreeSurfer were extracted from multiple cortical automatic parcellations (“aparc”, “aparc.a2009s”, and “aparc.DKT40”). Thus, brain measurements include some from overlapping regions in our datasets. These annotation formats were manually made with 34 cortical regions per hemisphere from 40 participants according to a sulcus approach, 74 cortical regions per hemisphere from 24 participants according to anatomical conventions, and 40 cortical regions per hemisphere from 101 participants according to a surface-based approach in Desikan/Killiany Atlas (“aparc”), Destrieux Atlas (“aparc.a2009s”), and Desikan–Killiany–Tourville atlas (“aparc.DKT40”), respectively. Because *pros* and *cons* of these annotation atlases have not been established as a consensus, we analyzed all data from the three atlases.

Our results demonstrated DS-associated abnormal cortical development in the right rostral ACC, right STC, and left MFC. Since we are reporting decreased cortical thickness variability in DS, we would like to assess whether or not this finding is associated with regional cortical dysfunction. Direct evidence that decreased variation of regional cortical thickness is associated with regional cortical malfunction has not been reported. In our previous work using neurotypical controls, as the age increased from toddlers to adulthood, the SD of the left rostral MFC thickness decreased from 0.86 to 0.66 in males and from 0.85 to 0.68 in females.[10] Our results showed that DS patients had decreased regional variation (SD) of cortical thicknesses when compared to NC. Although in typical development,

decreased regional variation of cortical thickness with age may be related to normal brain maturation involving cortical folding, myelination, neural remodeling, and synaptic pruning,[22] it is unlikely that these maturation processes are accelerated in DS.[3] In our study decreased SD of thicknesses of the right rostral ACC, right STC, and left MFC were observed in DS, which may be related to a decreased degree of neuronal migration and myelination in the cortex of those regions.[4] The ACC is a part of the limbic system. The dorsal part of the ACC is related to visual cognition and emotion such as anxiety.[23] The STC includes auditory association areas, and plays a crucial role in the processing of auditory and visual speech information,[24] and internal timing when communicating with others.[25] The MFC plays a role in the down-regulation of emotional responses,[26] reorienting of attention,[27] and hand writing symbolic codes such as letters and words.[28] The regional cortical changes observed in this study potentially contribute to intellectual dysfunction in DS found in the literature.

An additional perspective is that regional cortical changes might be secondary to cerebellar volume loss. The volumes of the bilateral cerebellar GM in DS were already abnormally decreased at birth (Fig. 1) and continued to be significantly reduced compared to NC throughout the studied age period. The volumes of the right ACC and the right STC initially had similar values in DS and NC, with group-wise differences gradually increasing and demonstrating statistically significantly reduced volumes in DS in later developmental stages. Recent functional MRI studies revealed cortico-cerebellar functional networks of the ACC and STC with the cerebellum.[29–31] The hypoactivities in these cortico-cerebellar pathways due to the small cerebellum might contribute to decreased volume of the ACC and STC as secondary effects.

Limitations

In the current study, we did not include the assessment of neurocognitive functions in DS. Therefore, it is difficult to directly connect the findings in structural MRIs with cognitive dysfunction in DS. Some researchers have looked at potential pathways to connect structural differences and various neuroanatomic features with characteristic neurocognitive profiles in DS.[32–34] Although some patterns emerge as a population, prediction of individual neurocognitive outcomes based on neuroimaging is not currently possible. Therefore, further research is needed in this area.

Furthermore, in this study, rates of comorbidities such as congenital cardiac disease and infantile spasms were higher than in prior prospective studies. The possible presence of selection bias (healthcare access bias) could not be excluded, because our study is retrospective and performed at a single medical facility. In addition, as a common issue among DS studies, our control population did not have comorbidities associated with DS. In the future, it would be important to use data from patients with such comorbidities without DS diagnoses (e.g. congenital cardiac disorders) in order to control for these comorbidities in DS.

An additional limitation of this study is that FreeSurfer[12] is not optimized for the youngest participants. As such, the rate at which FreeSurfer fails to extract measurements from clinical MRI examinations increases substantially for participants aged 0 to 8 months and

the reliability of the results successfully produced by FreeSurfer on participants from this age range is not certain. FreeSurfer's reliability was assessed as reasonable for participants 8-months-old and later,[10,35] at which point myelination contrast patterns have inverted so as to match the general pattern exhibited through the rest of life. Research aimed at overcoming the problem of FreeSurfer's applicability and reliability in very young populations is ongoing[36] and developments in this venue will be incorporated into future work.

5. CONCLUSION

We analyzed structural MRI in infants and toddlers with DS, and found that cerebellar GM volumes and brainstem volume were reduced in infants with DS relative to NC, an effect that was independent of patient comorbidities. These results suggest that cerebellar GM and the brainstem might be the regions primarily affected by an extra copy of chromosome 21 during early brain development.

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Abbreviations

DS	Down syndrome
NC	Neurotypical controls
MRI	magnetic resonance imaging
YO	years old
SD	standard deviation
GM	gray matter
WM	white matter
GI	gyrification index
GLM	General Linear Model
ACC	anterior cingulate cortex
STC	superior temporal cortex
MFC	middle frontal cortex

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Highlights

- A surface-based MRI analysis was carried out in infants and toddlers with DS.
- The effect of comorbid status in an early years DS population was assessed.
- The cerebellar gray matter is smaller in DS independently of comorbid effects.
- Regionally reduced variability of cortical thickness was observed in DS.

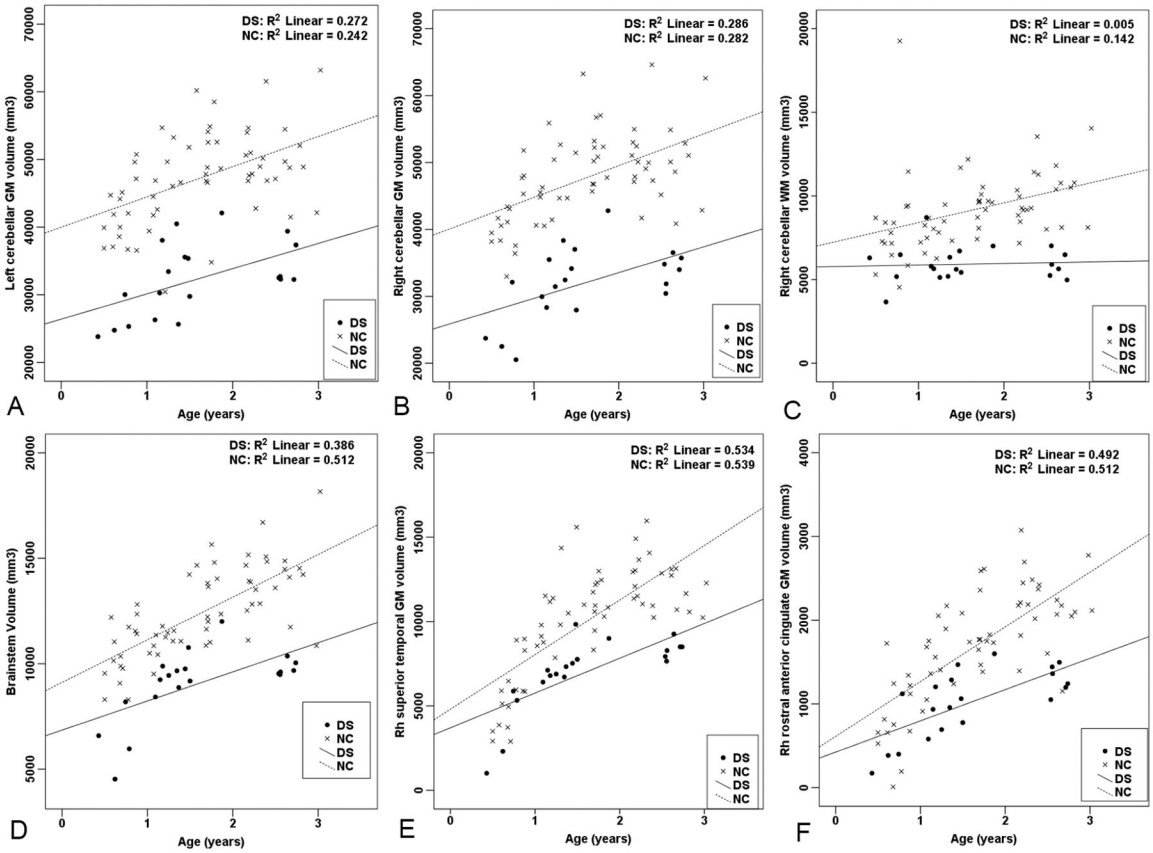

Figure 1.

Scatter plots and regression lines (between age vs. volume) of left (A) and right cerebellar GM (B), right cerebellar WM (C), brainstem (D), right superior temporal GM (E), and right rostral anterior cingulate GM (F) in DS (closed circle and solid-line) and NC (x and dot-line) participants. Abbreviation; DS, Down syndrome; NC, neurotypical controls; GM, gray matter; WM, white matter; Rh, right hemisphere.

Table 1

The background of Down syndrome and neurotypical control participants

	Down syndrome (N=20)	Neurotypical controls (N=60)
The rate of male (N [%])	13 / 20 [65%]	39 / 60 [65%]
Age of years (mean [SD])		
in total participants	1.6 [0.6]	1.6 [0.5]
in male participants	1.5 [0.5]	1.5 [0.5]
in female participants	1.8 [0.8]	1.8 [0.6]
Congenital cardiac disease (N [%])	15 / 20 [75%]	0 / 60 [0%]
Infantile spasm (N [%])	3 / 20 [15%]	0 / 60 [0%]
Hypothyroidism (N [%])	6 / 20 [30%]	0 / 60 [0%]

Abbreviation; SD, standard deviation

Table 2

Global brain volumes in DS and NC participants

Measurement	DS (N = 20) Mean [SD]	NC (N = 60) Mean [SD]	The rate of DS/NC	t	df	*p* value	Absolute Cohen's *d*
Category; aseg							
Estimated total intracranial volume (mm^2)	927348 [171768]	1083446 [195133]	0.86	−3.2	78	0.0021	0.82
Total cortical GM volume (mm^2)	360050 [104933]	426319 [118838]	0.84	−2.2	78	0.029	0.57
Total cortical WM volume (mm^2)	219022 [44640]	247444 [69445]	0.89	−2.1	51.3	0.039	0.44
Total subcortical GM volume (mm^2)	37461 [8274]	42244 [9685]	0.89	−2.0	78	0.051	0.51

Abbreviation; DS, Down syndrome; NC, neurotypical controls; SD, standard deviation; GM, gray matter; WM, white matter

Table 3

Candidate brain morphologic measurements in DS and NC participants

Measurement	DS (N=20) Mean [SD]	NC (N = 60) Mean [SD]	The rate of DS/NC	t	df	*p* value	Absolute Cohen's *d*
Annotation format; aseg							
Left cerebellar GM, volume (mm^3)	32372 [5461]	47260 [6653]	0.68	−9.0	78	9.3×10^{-14}	2.33
Right cerebellar GM, volume (mm^3)	32007 [5489]	47761 [6539]	0.67	−9.7	78	5.1×10^{-15}	2.50
Right cerebellar WM, volume (mm^3)	5924 [1036]	9149 [2288]	0.65	−8.6	70.8	1.4×10^{-12}	1.57
Brainstem, volume (mm^3)	9061 [1694]	12399 [2069]	0.73	−6.5	78	6.5×10^{-9}	1.68
Annotation format; aparc							
Lh rostral middle frontal ThickStd (mm)	0.73 [0.08]	0.89 [0.17]	0.82	−5.8	70	2.1×10^{-7}	1.06
Rh rostral middle frontal ThickStd (mm)	0.74 [0.071]	0.89 [0.16]	0.83	−5.7	71.9	2.3×10^{-7}	1.04
Rh rostral anterior cingulate SurfArea (mm^2)	215.1 [73.3]	356.4 [146.0]	0.6	−5.6	65.7	4.5×10^{-7}	1.07
Rh rostral anterior cingulate GM, volume (mm^3)	865 [379]	1470 [639]	0.59	−5.1	56.4	4.6×10^{-6}	1.03
Rh superior temporal GM, volume (mm^3)	7000 [2152]	10063 [3229]	0.70	−4.8	49.3	1.5×10^{-5}	1.02
Lh rostral anterior cingulate GM, volume (mm^3)	1080 [442]	1751 [848]	0.62	−4.4	60.1	4.0×10^{-5}	0.87
Rh supramarginal gyrus, SurfArea (mm^2)	2242 [465]	2883 [846]	0.78	−4.3	60.4	7.4×10^{-5}	0.83
Annotation format; aparc.a2009							
Lh inferior frontal sulcus, ThickStd (mm)	0.55 [0.11]	0.73 [0.22]	0.75	−4.9	64.2	7.9×10^{-6}	0.93
Lh anterior part of the cingulate gyrus and sulcus, SurfArea (mm^2)	772 [212]	1087 [392]	0.71	−4.5	61.2	2.8×10^{-5}	0.88
Rh supramarginal gyrus, SurfArea (mm^2)	1095 [178]	1492 [427]	0.73	−5.8	74.1	1.3×10^{-7}	1.04
Rh lateral aspect of the superior temporal gyrus, SurfArea (mm^2)	709 [146]	938 [254]	0.76	−4.9	57.7	7.2×10^{-6}	0.98
Rh inferior segment of the circular sulcus of the insula GM, volume (mm^3)	1223 [302]	1720 [416]	0.71	−4.9	78	4.8×10^{-6}	1.27
Rh inferior frontal sulcus, ThickStd (mm)	0.58 [0.10]	0.74 [0.21]	0.78	−4.6	66.2	2.3×10^{-5}	0.86
Rh transverse temporal sulcus, SurfArea (mm^2)	107 [36]	159 [65]	0.67	−4.4	56.5	4.3×10^{-5}	0.88
Lh frontal superior gyrus, SurfArea (mm^2)	2641 [505]	3399 [1056]	0.78	−4.3	68.1	6.0×10^{-5}	0.80
Annotation format; aparc.DKTatlas40							
Lh rostral middle frontal GM, ThickStd (mm)	0.74 [0.08]	0.89 [0.2]	0.82	−5.7	71.7	2.6×10^{-7}	1.03
Rh rostral middle frontal GM, ThickStd (mm)	0.73 [0.07]	0.88 [0.17]	0.83	−5.5	73.6	4.8×10^{-7}	0.99
Rh superior temporal GM, SurfArea (mm^2)	2745 [608]	3626 [967]	0.76	−4.8	52.5	1.5×10^{-5}	0.99
Rh rostral anterior cingulate GM, SurfArea	251 [77]	406 [149]	0.62	−6.0	64.3	1.2×10^{-7}	1.15

Measurement	DS (N=20) Mean [SD]	NC (N = 60) Mean [SD]	The rate of DS/NC	t	df	*p* value	Absolute Cohen's *d*
(mm^2)							
Rh rostral anterior cingulate GM, volume (mm^3)	1022 [406]	1695 [663]	0.60	−5.4	54.6	1.8×10^{-6}	1.10
Rh supramarginal GM, SurfArea (mm^2)	2140 [438]	2765 [790]	0.77	−4.4	59.9	4.3×10^{-5}	0.87
Lh caudal anterior cingulate GM, ThickStd	0.66 [0.18]	0.90 [0.28]	0.74	−4.3	51.7	8.3×10^{-5}	0.89
(mm)							
Lh rostral anterior cingulate GM, volume (mm^3)	1376 [643]	2217 [1066]	0.62	−4.2	55.2	9.6×10^{-5}	0.86

Abbreviation; DS, Down syndrome; NC, neurotypical controls; SD, standard deviation; GM, gray matter; WM, white matter; Lh, left hemisphere; Rh, right hemisphere; SurfArea, Surface Area; ThickStd, Thickness standard deviation

Table 4

The effects of covariates on candidate brain morphologic measurements; Univariate General Linear Model

	Adjusted *R* squire	Corrected Model	DS	Age	Gender	Congenital Cardiac disease	Infantile spasm	Hypothy roidism
Annotation format; aseg								
Left cerebellar GM, volume	.638	**F = 24.2**	**F = 10.8**	**F = 24.9**	F = 2.4	F = 2.2	F = 1.5	F = .31
		$p = 1.5 \times 10^{-15}$	**$p = .002$**	**$p = 4.0 \times 10^{-6}$**	$p = .13$	$p = .14$	$p = .22$	$p = .58$
Right cerebellar GM, volume	.682	**F = 29.2**	**F = 11.9**	**F = 32.1**	F = 3.6	F = 3.1	F = .38	F = 1.8
		$p = 1.5 \times 10^{-17}$	**$p = .001$**	**$p = 2.8 \times 10^{-7}$**	$p = .06$	$p = .08$	$p = .54$	$p = .18$
Right cerebellar WM, volume	.387	**F = 9.3**	**F = 9.0**	**F = 12.4**	**F = 4.1**	F = .14	F = .13	F = 1.2
		$p = 1.4 \times 10^{-7}$	**$p = .004$**	**$p = .001$**	**$p = .047$**	$p = .71$	$p = .72$	$p = .28$
Brainstem, volume	.654	**F = 25.9**	**F = 9.6**	**F = 69.7**	F= 2.9	F = .68	F = .35	F = .68
		$p = 2.8 \times 10^{-16}$	**$p = .003$**	**$p = 3.1 \times 10^{-12}$**	$p = .09$	$p = .41$	$p = .56$	$p = .41$
Annotation format; aparc								
Lh rostral middle frontal ThickStd	.325	**F = 7.35**	**F = 5.6**	**F = 21.6**	F = .67	F = .16	F = .99	F = .26
		$p = 3.6 \times 10^{-6}$	**$p = .02$**	**$p = 1.5 \times 10^{-5}$**	$p = .42$	$p = .70$	$p = .32$	$p = .61$
Rh rostral middle frontal ThickStd	.226	**F = 4.6**	F = 3.4	**F = 9.9**	F = .26	F = .004	F = .17	F = .009
		$p = 3.2 \times 10^{-4}$	$p = .068$	**$p = .002$**	$p = .62$	$p = .95$	$p = .68$	$p = .92$
Rh rostral anterior cingulate SurfArea	.517	**F = 14.8**	**F = 5.0**	**F = 55.2**	F = .76	F = .06	F = .04	F < .01
		$p = 7.3 \times 10^{-11}$	**$p = .03$**	**$p = 1.9 \times 10^{-10}$**	$p = .39$	$p = .81$	$p = .84$	$p = .99$
Rh rostral anterior cingulate GM, volume	.529	**F = 4.9**	F = 3.7	**F = 59.0**	F = .23	F = .27	F = .02	F = .008
		$p = 3.2 \times 10^{-4}$	$p = .057$	**$p = 6.6 \times 10^{-11}$**	$p = .59$	$p = .61$	$p = .88$	$p = .93$
Rh superior temporal GM, volume	.580	**F = 19.2**	**F = 5.4**	**F = 78.1**	F = .53	F = .03	F = 1.4	F = .19
		$p = 2.8 \times 10^{-13}$	**$p = .023$**	**$p = 3.7 \times 10^{-13}$**	$p = .47$	$p = .86$	$p = .25$	$p = .67$
Lh rostral anterior cingulate GM, volume	.471	**F = 12.7**	F = 3.3	**F = 57.1**	F = 0.1	F = .02	F = .02	F < .01
		$p = 8.7 \times 10^{-10}$	$p = .075$	**$p = 9.6 \times 10^{-11}$**	$p = .82$	$p = .88$	$p = .90$	$p = .93$
Rh supramarginal gyrus, SurfArea	.373	**F = 8.8**	F = .90	**F = 36.3**	**F = 4.2**	F = .23	F = .058	F = 1.9
		$p = 3.1 \times 10^{-7}$	$p = .35$	**$p = 6.3 \times 10^{-8}$**	**$p = .044$**	$p = .63$	$p = .81$	$p = .17$
Annotation format; aparc.a2009								
Lh inferior frontal sulcus, ThickStd	.176	**F = 3.8**	F = 2.1	**F = 7.8**	F = .20	F = .006	F = .73	F = .03
		$p = .002$	$p = .16$	**$p = .007$**	$p = .66$	$p = .94$	$p = .40$	$p = .86$

	Adjusted R^2 squire	Corrected Model	DS	Age	Gender	Congenital Cardiac disease	Infantile spasm	Hypothy roidism
Lh anterior part of the cingulate gyrus and sulcus, SurfArea	.499	**F = 14.1**	F = 2.7	**F = 57.2**	F = .008	F = .40	F = 1.3	F = .06
		$p = 1.3 \times 10^{-10}$	p = .10	$p = 9.3 \times 10^{-11}$	p = .93	p = .53	p = .27	p = .82
Rh Supramarginal gyrus, SurfArea	.452	**F =11.9**	F = 3.0	**F = 42.2**	**F = 10.6**	F = .02	F = .04	F = 2.3
		$p = 3.0 \times 10^{-9}$	p = .09	$p = 8.7 \times 10^{-9}$	p = .002	p = .89	p = .85	p = .14
Rh lateral aspect of the superior temporal gyrus, SurfArea	.404	**F = 9.9**	F = 1.8	**F = 36.1**	F = 1.2	F = .27	F = .42	F = .58
		$p = 5.6 \times 10^{-8}$	p = .19	$p = 6.7 \times 10^{-8}$	p = .28	p = .61	p = .52	p = .45
Rh inferior segment of the circular sulcus of the insula GM, volume	.331	**F = 7.5**	F = 3.8	**F = 15.8**	F = .08	F = .11	F = .08	F = .19
		$p = 2.7 \times 10^{-6}$	p = .054	$p = 1.6 \times 10^{-4}$	p = .78	p = .74	p = .79	p = .66
Rh frontal inferior sulcus, ThickStd	.162	**F = 3.5**	F = 2.1	**F = 8.4**	F < .01	F < .01	F = .73	F = .93
		$p = 3.9 \times 10^{-3}$	p = .15	$p = 5.1 \times 10^{-3}$	p = .95	p = .93	p = .40	p = .76
Rh transverse temporal sulcus, SurfArea	.340	**F = 7.8**	F = .33	**F = 28.5**	F = 1.7	F = .56	F = .36	F = 3.3
		$p = 1.7 \times 10^{-6}$	p = .57	$p = 1.0 \times 10^{-6}$	p = .20	p = .46	p = .55	p = .075
Lh frontal superior gyrus, SurfArea	.560	**F = 17.8**	F = 2.5	**F = 82.4**	F = .70	F = .74	F = .68	F = .91
		$p = 1.4 \times 10^{-12}$	p = .12	$p = 1.3 \times 10^{-13}$	p = .11	p = .68	p = .41	p = .34
Annotation format; aparc.DKTatlas40								
Lh rostral middle frontal GM, ThickStd	.293	**F = 6.4**	**F = 4.8**	**F = 18.7**	F = .99	F = .05	F = .32	F = .17
		$p = 1.7 \times 10^{-5}$	p = .03	$p = 4.9 \times 10^{-5}$	p = .32	p = .82	p = .57	p = .68
Rh rostral middle frontal GM, ThickStd	.173	**F = 3.8**	F = 3.1	**F = 6.4**	F = .08	F < .01	F = .31	F = .04
		p = .003	p = .08	p = .013	p = .77	p > .99	p = .58	p = .85
Rh superior temporal GM, SurfArea	.536	**F = 16.2**	F = 1.8	**F = 63.9**	F = .28	F = 1.0	F = .005	F = .36
		$p = 9.1 \times 10^{-12}$	p = .18	$p = 1.5 \times 10^{-11}$	p = .60	p = .32	p = .94	p = .55
Rh rostral anterior cingulate GM, SurfArea	.522	**F = 15.0**	**F = 6.3**	**F = 53.7**	F = .44	F = .02	F = .69	F = .046
		$p = 5.1 \times 10^{-11}$	p = .014	$p = 3.0 \times 10^{-10}$	p = .51	p = .89	p = .41	p = .83
Rh rostral anterior cingulate GM, volume	.554	**F = 16.9**	**F = 4.3**	**F = 63.2**	F = .13	F = .28	F = .05	F = .08
		$p = 4.9 \times 10^{-12}$	p = .042	$p = 2.1 \times 10^{-11}$	p = .72	p = .60	p = .83	p = .78
Rh supramarginal GM, SurfArea	.375	**F = 8.9**	F = .97	**F = 35.1**	**F = 5.1**	F = .30	F = .028	F = 1.8
		$p = 2.7 \times 10^{-7}$	p = .33	$p = 9.4 \times 10^{-8}$	p = .027	p = .58	p = .87	p = .18
Lh caudal anterior cingulate GM, ThickStd	.099	**F = 2.4**	F = 3.6	F = .25	F = 2.3	F = .011	F = .05	F = 1.2

	Adjusted *R* squire	Corrected Model	DS	Age	Gender	Congenital Cardiac disease	Infantile spasm	Hypothy roidism
		***p* = .033**	*p* = .06	*p* = .62	*p* = .13	*p* = .92	*p* = .82	*p* = .27
Lh rostral anterior cingulate GM, volume	.501	**F = 14.2**	F = 3.2	**F = 62.1**	F < .01	F < .01	F = .012	F < .01
		***p* = 1.2 × 10^{-10}**	*p* = .077	***p* = 2.4 × 10^{-11}**	*p* = .95	*p* = .97	*p* = .91	*p* = .99

Bold indicates values with a statistically significance. Abbreviation; DS, Down syndrome; NC, neurotypical controls; GM, gray matter; WM, white matter; Lh, left hemisphere; Rh, right hemisphere; SurfArea, Surface Area; ThickStd, Thickness standard deviation