



# Anatomical MRI study of global & focal developmental delay in infants (<2 years old)

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## Abstract

**Objective:** To use structural magnetic resonance imaging (3D-MRI) to evaluate the abnormal development of the cerebral cortex in infants with global developmental delay (GDD).

**Methods:** The GDD group includes 67 infants aged between 112 and 699 days with global developmental delay and who underwent T1-weighted MRI scans in Icare institute from 2016 to 2019. The healthy control (HC) group includes 135 normal developing infants aged between 88 and 725 days in hospital from 2016 to 2019. Whole-brain T1-weighted MRI scans were carried out with a 1.5 -T magnetic resonance scanner, which was later processed using InfantSurfer to perform MR image processing and cortical surface reconstruction. Two morphological features of the cortical surface of the 68 brain regions were computed, i.e., the cortical thickness (CT) and cortical surface area (SA), and compared between the GDD and HC groups.

**Results:** With regard to the CT, the HC group showed a rapid decrease at first and then a slow increase after birth, and the CT of the GDD group decreased slowly and then became relatively stable. The GDD group showed bilaterally higher hemispherical average CT than those in the HC group. In detail, for the left hemisphere, except in the entorhinal and temporal poles in which the average CT values of the two brain regions were lower than those of the HC group, the CT of the 26 brain regions in the GDD group was higher than those of the HC group ( $p < 0.05$ ). For the right hemisphere, the CT of the entorhinal in the GDD group was lower than that in the HC group. Otherwise, the CT of the remaining 28 brain regions was higher than those in the HC group ( $p < 0.05$ ). With regard to the SA, both groups showed a rapid increase after birth till 23 months and remained quite stable afterward. The GDD group shows lower SA bilaterally than that in the HC group. In detail, SA in the GDD group was lower in most cortical regions of both hemispheres than in the HC group ( $p < 0.05$ ), except for the right temporal pole and entorhinal. When testing for brain asymmetry, we found that the HC group showed obvious asymmetry of CT and SA, while only a few cortical regions in the GDD group showed asymmetry.

**KEYWORDS:** global developmental delay, infant, cortical surface, CT, SA, MRI

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## Introduction

(DSM-V) issued by the American Psychiatric Association

The diagnostic criteria of the 5th edition of the on 18 May 18 2013 classify global developmental delay Diagnostic and Statistical Manual of Mental Disorders (GDD) as a neurodevelopmental disorder, which refers



to underdevelopment in more than two aspects, volume, cortical thickness, and surface area. Cortical including skills like motor, language, cognitive and thickness (CT) and surface area (SA) are important social communication, and adjusts the diagnostic age to components that measure cortical morphometry. CT <5 years old (1). The prevalence of GDD is around 3%, and SA abnormalities are commonly observed in and 5–10% of healthy children experience GDD early neurodevelopmental

in development. Most cases often have several causes, disorders, including bipolar disorder (9), which are mutually transformed and causative. There schizophrenia (10), autism (11), and attention- is a study that has shown that GDD is associated with deficit/hyperactivity disorder (12). Shaw et al. used genetic defects (2), and Li et al. show the subtle 3D-T1WI's longitudinal study of the correlation structural changes of each brain area in children between intelligence and cortical thickness in normal with GDD by the change of ADC value (3) to indirectly children and adolescents and found that in early understand the location and degree of brain injury in childhood, there was a significant negative correlation children. In a functional imaging study, the UF and SCP between intelligence and cortical thickness, while with WMT showed microstructural changes suggestive of age, they gradually showed a positive correlation compromised white matter maturation in children (13). Therefore, the selection of these two indicators with GDD (4). Current international scientific research for quantitative analysis of children with GDD is and clinical evaluation of GDD is mostly based on helpful to further explore the relevant the Gesell development diagnosis scale, which pathophysiological mechanism.

evaluates the development in five aspects, such as An MRI can associate the development of the brain gross movement, fine movement, speech, human structure with the behavior of infants, making it ability, and response-ability. The infant is diagnosed convenient to evaluate the lesions. In particular, 3D- with GDD when the development quotient (DQ) is MRI uses three-dimensional volume scanning with lower than 70 in two or more aspects. The current high spatial resolution and good tissue contrast and research regards the age of 0–3 as the key period for can display brain structure at the submillimeter level, the early identification of infants with GDD. Lack of which is convenient for the establishment of a visual early diagnosis and intervention may introduce further map of the human brain. Infant FreeSurfer (14) is the intellectual disability, such as cerebral palsy, autism most advanced special cortex analysis software for spectrum disorder (ASD), or attention deficit infants, which can calculate the morphological hyperactivity disorder (ADHD) (5). In particular, the parameters of any position of the brain or other development of language is combined with cognition, related data. The purpose of this study is to which is proceeded for up to 21 months. After 3 years quantitatively analyze the CT and SA of infants with old, cognitive and language development training GDD by using whole- brain 3D-MRI, draw the becomes more difficult, recovery is slow, and the developmental trajectory maps, and analyze the possibility of curing children with GDD is significantly hemispheric asymmetry to help find the brain reduced (6). The diagnosis and imaging study of the structural changes related to the disease and further GDD is of great significance to the choice of reveal the potential pathophysiological mechanism of treatment, prognosis, risk assessment of recurrence, GDD.

and the implementation of prevention programs. At Global developmental delay is a temporary present, few studies are focusing on GDD with whole- diagnosis, which can be returned to normal after a brain structure MR images. timely clinical intervention. The use of structural

The first 2 years of life are a period of abnormal magnetic resonance imaging (3D-MRI) to evaluate dynamic development of the structure and functions the abnormal development of the cerebral cortex in of the human brain. Babies' brains reach 80% of children with global developmental delay is their adult size at the age of 2 conducive to providing early imaging evidence for the (7). Studies have shown that many clinic and analyzing the differences in different brain neurodevelopmental and mental disorders are regions, providing support for the study of the caused by abnormal brain development at this stage. mechanism of related neuropsychiatric disorders.

The cerebral cortex, which makes up the largest part of the human brain, has the topology of a 2-D sheet Data and methods and a highly folded geometry (8). Surface-based General information morphometry (SBM) is widely used and mature in The experimental group selected 67 infants who estimating cortical morphological indexes such as underwent 3D-T1WI MRI examination in Hospital as



the GDD group. They were aged between 112 and 699 d and included the following criteria: (1) met the diagnostic criteria of GDD in DSM-V; (2) the age was between 0 and 2 years old; (3) there was no previous neurotrophic factor drug therapy; (4) the image quality was good, and accurate data could be obtained. Exclusion criteria: infantile schizophrenia, obsessive-compulsive disorder, autism spectrum disorder, Asperger's syndrome, and other diseases. In the HC group, 145 infants were selected who underwent T1-weighted brain MRI examination in Icare hospital from 2016 to 2019, aged from 88 to 725 days. Inclusion criteria were as follows: (1) full-term natural delivery; (2) no family history of mental or neurological disease; (3) no intracranial space occupying or congenital disease by clinical and imaging examination; (4) normal motor and cognitive function tested by anatomical development scale. All children were examined under sedation. This study was approved by the ethics committee of Icare Hospital.

#### Inspection method

For the 3D-T1WI data collection, all subjects were given an enema with 5% chloral hydrate, a dose of 1 ml/kg, equipped with a hearing protection device, and scanned after deep sleep.

The GDD group was examined with GEDISCOVERY MR750W3.0T magnetic resonance machine and the head matrix coil. Sweep parameters were as follows: (1) regular MRI: T1WI:

TR = 1,750 ms, TE = 27 ms; T2WI: TR = 5,231 ms, TE = 129 ms; T2-FLAIR: TR = 7,800 ms, TE = 89 ms.

*All sequences:*

FOV = 200 × 200 mm<sup>2</sup>, matrix = 256 × 256 mm<sup>2</sup>, slice spacing = 1.2 mm, slice thickness = 5.0 mm, excitation times = 2.

(2) 3D-T1WI sequence: TR = 7.7 ms, TE = 2.8 ms, FOV = 240 × 240 mm<sup>2</sup>, matrix = 256 × 256 mm<sup>2</sup>, slice spacing = 0 mm, slice thickness = 1.0 mm, excitation times = 1.

The HC group was examined with Philips Achieva 1.5T magnetic resonance machine and the head matrix coil. MR scan sequences include: (1) 3D-T1WI: using gradient echo

sequence, TR = 600 ms, TE = 27 ms, FOV = 250 × 250 mm<sup>2</sup>, slice spacing = -0.55 mm, slice thickness = 1.1 mm. (2) T2WI: TR = 2,651 ms, TE = 105 ms, FOV = 180 × 180 mm<sup>2</sup>, matrix = 0.9 × 0.9 mm<sup>2</sup>, slice spacing = 0.5 mm, slice thickness = 4.0 mm, excitation times = 2.

#### Data processing

In this experiment, the Infant FreeSurfer software (11) was used to reconstruct the three-dimensional cortical surface of all 3D-T1WI magnetic resonance image data, including image intensity correction, head stripping, brain tissue segmentation, left and right cerebral dissection, reconstruction of the inner and outer surface of the cerebral cortex, and so on. To ensure the quality of skull dissection and the accuracy of gray matter/white matter boundary segmentation, the results of skull dissection and brain tissue segmentation were examined by two skilled anatomical operators. After the cortical reconstruction was completed, the left and right hemispheres were divided into 33 brain regions according to the FreeSurfer cortical atlas (15), and the average CT and the summed SA of each brain region were calculated. Linear mixed effect (LME) (16) models were used to model the development trajectory, and three

models (linear, quadratic, and logistic curve) were used to fit the trajectory. After fitting different models, the best model was selected as the development trajectory according to the Akaike Information Criterion (AIC). In this study, based on this model, the developmental trajectories of CT and SA of two groups of subjects with age were fitted, respectively.

MATLAB software was used to analyze the differences in the CT and SA between the two groups and the asymmetry between the left and right hemispheres of the two groups. Double-sample unpaired *t*-test was used for the difference between the groups, and paired *t*-test was used for hemispheric asymmetry. *P* < 0.05 was statistically significant.

#### Results

##### Developmental trajectories of CT

Figure 1 shows the comparative maps of the CT developmental trajectory of bilateral cerebral hemispheres between the two groups. Figure 2 shows the CT developmental trajectories of some representative regions of the two groups. Red represents the HC group and the blue line represents the GDD group. Different from the trend of rapid



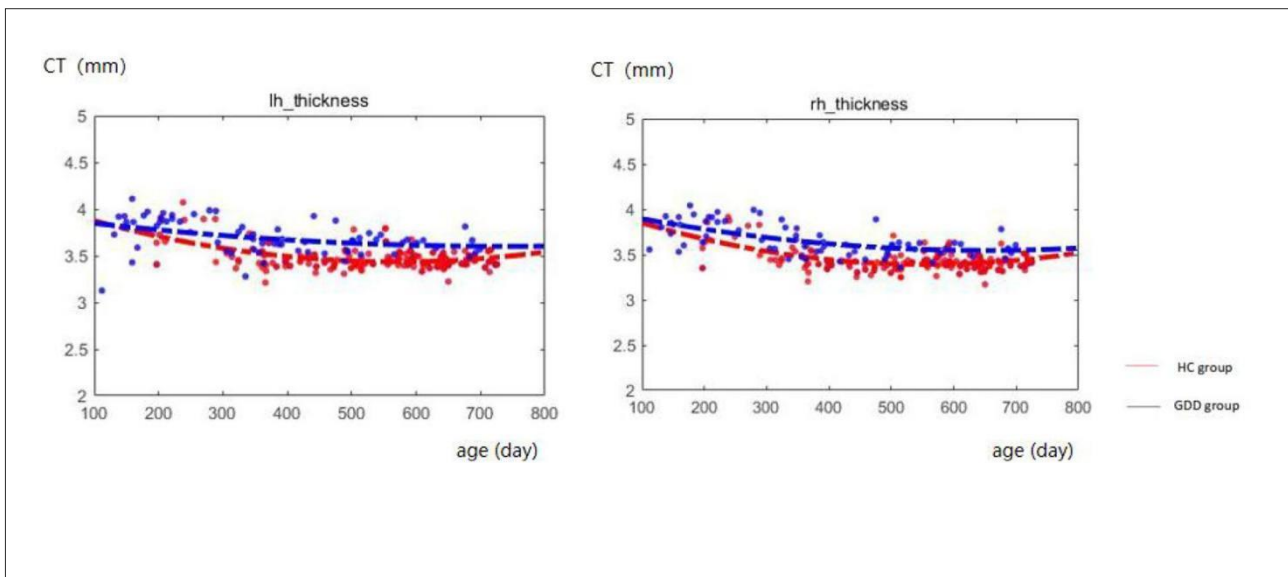
decrease and then slow increase of average CT in the HC group, the average CT of the GDD group decreases slowly and then remains stable. From the developmental trajectory maps, it can be seen that the average CT values of both sides of the brain in the GDD group are higher than those in the HC group.

**Developmental trajectories of SA**

Figure 3 shows the comparative maps of the hemispherical SA developmental trajectory between the two groups. Figure 4 shows the SA developmental trajectories of some representative regions of the two groups. Red represents the HC group and the blue line represents the GDD group. The average SA of both groups increases rapidly at first, reaches the peak at about 23 months, and then remains stable. From the developmental trajectory maps, it can be seen that the average SA value of both sides of the brain in the GDD group is lower than that in the HC group

**Differences in CT between two groups**

Table 1 shows brain regions with significant differences in cortical thickness (CT) of bilateral cerebral hemispheres between the two groups. As shown in Table 1, for the left cerebral hemisphere, except for the average CT values of the entorhinal and temporal pole are lower than that of the HC group, the CT values of 26 brain regions such as caudal middle frontal, postcentral, pars-triangularis, supra-marginal, and bankssts in the GDD group are higher than those of the HC group, while for the right cerebral hemisphere, except that the CT value of entorhinal is lower than that of the HC group, the CT values of 28 brain regions such as superior temporal, posterior cingulate, inferior parietal, precentral and transverse temporal in the GDD group are higher than those of the HC group.



**Differences in SA between two groups**

Table 2 shows brain regions with significant differences in cortical surface areas (SA) of bilateral cerebral hemispheres

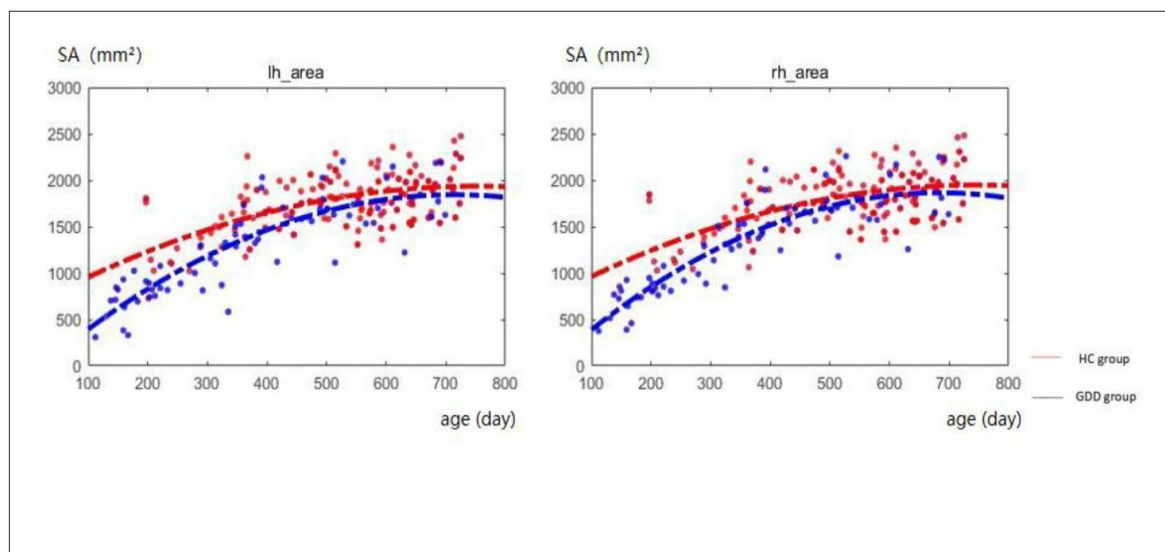
between the two groups. As shown in Table 2, for the left hemisphere, SA values in all 33 brain regions in the GDD group are lower than those in the HC group; for the right hemisphere, SA values in 31 brain regions in the GDD group are also lower than those

in the HC group, except the entorhinal and temporal pole.

**Asymmetry of CT and SA of the two groups**

The medial and lateral views of Figures 5A,C show the asymmetry of CT and SA between the left and right hemispheres of the HC group. The medial and lateral views of Figures 5B,D show the asymmetry of CT and SA between the left and right hemispheres of the GDD group. All results are shown.





on the average central cortical surface of the age-participate in the realization of cognitive and matched left hemisphere. On the medial and lateral sensory functions. Developmental disorders in any surfaces, the overall patterns in the left greater than part of the cerebral cortex can lead to motor, the right (red), and the right greater than the left language, and cognitive disorders. (blue) are relatively consistent in all ages.

As shown in Figure 5B and Table 3, the significantly At present, there are various forms of research on the asymmetric brain regions of CT in the GDD group are cerebral cortex, and surface-based morphometry the lateral orbitofrontal, pars-orbitalis, pericalcarine, (SBM) is more in line with the goal of this study. We and posterior cingulate, all of which are larger on the selected two indexes: cortical thickness and cortical left side than on the right side.

As shown in Figure 5D and Table 4, the significantly that cortical thickness and cortical surface area are asymmetric brain regions of SA in the GDD genetically related, but there is no genetic relationship group are pars-triangularis, pars-orbitalis, frontal between them (18), which further proves that they pole, caudal anterior cingulate, and transverse are indeed driven by different cellular mechanisms, temporal, all of which are larger on the right side which is consistent with the results of Rakic (16, than on the left side except transverse temporal. 19). There have been similar studies on the properties Comparing Figures 5A,C with Figures 5B,D, it can be of normal human brain structural networks, which seen that the asymmetry area of the brain in the have proved that the description of surface area and GDD group is less than that in the HC group. Except cortical thickness reveal different properties of human that the CT of the pericalcarine in the GDD group is brain network structures (20). Grasby et al. showed other brain regions is consistent with that of the HC area and thickness and observed that there was a group. significant positive genetic correlation and two-way causality between total surface area and general cognitive function and education level, and a

#### Discussion

As we all know, the development of the cerebralsignificant negative correlation between total surface cortex is closely related to the realization of variousarea and insomnia, attention deficit hyperactivity functions of the human body. For example, thedisorder, depressive symptoms, major depressive frontal lobe is the area of executive function,disorder, and neuroticism (21). Therefore, this study attention, and motor coordination; the parietalcompared the normal development of infants from lobe is involved in the development of spatialthe results of statistical differences between the two orientation, speech and language, and attention; the indicators, respectively, to explore the mechanism of temporal lobe is associated with memory integration;neurodevelopmental disorders related to general and the occipital lobe is the visual center (17), while developmental delay. the insular lobe connects the other lobes to



To eliminate the possible research differences GEDISCOVERYMR750W3.0T magnetic resonance caused by different scanning devices, machine in the study used the same data homogenization of the data of different devices processing method to compare the difference was carried out. We collected the image data of between CT and SA in each brain area of the same nineteen normally developing infants aged between bilateral brain. Only one of the brain regions on both 78 and 940 days who were examined by sides showed different results compared to existing GEDISCOVERYMR750W1.5.T magnetic resonance results, but the differences were not significant. In machine and met the inclusion criteria. The summary, we believe that the influence of different scanning parameters are the same as those of scanning devices on the research results can be GEDISCOVERYMR750W 1.5T magnetic resonance ignored. machine in the study. A new control group was formed between the above subjects and the control TABLE 2 Brain cortical regions that show significant subjects examined by PhilipsAchieva3.0T magnetic differences in cortical surface area (SA) between the resonance machine in the study. The new control two groups. group and the experimental group scanned by

Brain region SA (mm<sup>2</sup>)

	Left hemisphere (GDD/HC)		Right hemisphere (GDD/HC)			Left hemisphere (GDD/HC)		Right hemisphere (GDD/HC)	
	Left hemisphere (GDD/HC)	Right hemisphere (GDD/HC)	Left	Right		Left hemisphere (GDD/HC)	Right hemisphere (GDD/HC)	Left	Right
Caudal middle frontal	3.76/3.46	3.80/3.44	<0.0001**	<0.0001**	Caudal middle frontal	1087.77/1549.43	1132.23/1448.11	<0.0001**	<0.0001**
Entorhinal	2.27/3.08	2.56/3.07	<0.0001**	0.0005**	Entorhinal	123.46/164.58	172.18/151.78	0.0076**	0.5221
Postcentral	3.20/2.83	3.20/2.81	<0.0001**	<0.0001**	Postcentral	2713.43/3385.09	2839.90/3212.46	<0.0001**	<0.0001**
Pars triangularis	3.89/3.68	3.93/3.60	<0.0001**	<0.0001**	Pars triangularis	619.24/856.49	849.88/1022.06	<0.0001**	<0.0001**
Supra marginal	3.81/3.63	3.73/3.54	<0.0001**	<0.0001**	Supra marginal	2073.40/2682.30	2191.27/2560.47	<0.0001**	<0.0001**
Bankssts	3.74/3.51	3.85/3.58	<0.0001**	<0.0001**	Insula	1376.64/1669.19	1336.84/1566.32	<0.0001**	<0.0001**
Lateral orbitofrontal	4.11/4.12	3.84/3.92	0.9246	0.0464*	Bankssts	509.30/719.18	491.03/676.99	<0.0001**	<0.0001**
Pars orbitalis	4.22/4.03	4.02/3.90	<0.0001**	0.0112*	Lateral orbitofrontal	1095.04/1384.28	1373.65/1475.09	<0.0001**	<0.0001**
Middle temporal	4.05/3.74	4.09/3.78	<0.0001**	<0.0001**	Pars orbitalis	262.99/375.67	400.81/466.79	<0.0001**	<0.0001**
Pericalcarine	3.43/2.93	3.31/2.92	<0.0001**	<0.0001**	Middle temporal	1389.69/1991.66	1728.52/2211.28	<0.0001**	<0.0001**
Paracentral	3.61/3.22	3.66/3.27	<0.0001**	<0.0001**	Pericalcarine	640.50/971.46	786.29/1076.84	<0.0001**	<0.0001**
Medial orbitofrontal	4.03/4.05	4.09/3.99	0.799	0.0406*	Paracentral	842.28/1021.16	1014.06/1128.39	<0.0001**	<0.0001**
Frontalpole	4.51/4.37	4.52/4.38	0.0446*	0.0037**	Medial orbitofrontal	873.94/1048.12	943.83/1094.34	<0.0001**	<0.0001**
Cuneus	3.82/3.25	3.71/3.23	<0.0001**	<0.0001**	Frontalpole	120.06/158.83	190.28/206.51	<0.0001**	<0.0001**
Inferior temporal	4.04/3.68	4.05/3.69	<0.0001**	<0.0001**	Cuneus	721.13/1079.72	915.14/1137.95	<0.0001**	<0.0001**
Rostral middle frontal	4.12/3.74	4.08/3.70	<0.0001**	<0.0001**	Inferior temporal	1355.59/1951.14	1485.49/1877.82	<0.0001**	<0.0001**
Isthmus cingulate	2.91/2.66	2.86/2.62	<0.0001**	<0.0001**	Rostral middle frontal	2368.85/3392.16	2823.70/3521.96	<0.0001**	<0.0001**



Lateral occipital	3.86/3.16	3.81/3.16	<0.0001**	<0.0001**	Rostral anterior cingulate	369.22/498.77	370.93/464.99	<0.0001**	<0.0001**
Lingual	3.57/3.24	3.51/3.23	<0.0001**	<0.0001**	Isthmus cingulate	751.63/1056.92	802.35/1008.20	<0.0001**	<0.0001**
Superior parietal	3.73/3.26	3.70/3.23	<0.0001**	<0.0001**	Lateral occipital	2644.76/3719.88	2846.88/3600.93	<0.0001**	<0.0001**
Pars opercularis	3.80/3.58	3.83/3.54	<0.0001**	<0.0001**	Lingual	1409.71/2100.67	1695.88/2121.28	<0.0001**	<0.0001**
Fusiform	3.86/3.53	3.72/3.49	<0.0001**	<0.0001**	Superior parietal	3070.07/4349.31	3429.06/4196.36	<0.0001**	<0.0001**
Superior frontal	4.19/3.88	4.16/3.88	<0.0001**	<0.0001**	Pars opercularis	782.91/1094.37	775.27/968.42	<0.0001**	<0.0001**
Temporal pole	3.86/4.09	3.85/3.95	0.0018**	0.1032	Fusiform	1296.44/2002.08	1465.54/1932.85	<0.0001**	<0.0001**
Precuneus	3.92/3.52	3.81/3.51	<0.0001**	<0.0001**	Caudal anterior cingulate	373.16/464.14	479.48/570.34	<0.0001**	<0.0001**
Transverse temporal	3.26/3.09	3.31/3.15	<0.0001**	0.0002**	Superior frontal	3445.20/4450.62	3795.94/4287.15	<0.0001**	<0.0001**
Precentral	3.36/3.06	3.32/3.01	<0.0001**	<0.0001**	Temporal pole	251.08/297.65	308.28/266.77	0.0026**	0.9663
Inferior parietal	3.92/3.64	3.90/3.59	<0.0001**	<0.0001**	Precuneus	1900.47/2825.29	2326.39/3033.29	<0.0001**	<0.0001**
Posterior cingulate	3.37/3.13	3.17/2.91	<0.0001**	<0.0001**	Transverse temporal	294.05/372.20	241.71/294.85	<0.0001**	<0.0001**
Superior temporal	3.70/3.49	3.77/3.46	<0.0001**	<0.0001**	Precentral	2840.55/3590.41	3055.08/3590.00	<0.0001**	<0.0001**
Insula	3.73/3.68	3.76/3.72	0.14	0.2719	Inferior parietal	2187.09/3243.82	2868.38/3747.84	<0.0001**	<0.0001**
Rostral anterior cingulate	3.29/3.40	3.11/3.09	0.1156	0.6732	Posterior cingulate	712.06/928.79	790.42/957.84	<0.0001**	<0.0001**
Caudal anterior cingulate	3.05/3.03	2.99/2.92	0.7688	0.2132	Superior temporal	2155.62/2789.43	2304.05/2754.76	<0.0001**	<0.0001**

\*P < 0.05, \*\*P < 0.01.

\*\*P < 0.01.

### GDD and HC show different development trajectories

In this study, the average CT of the bilateral brain in the GDD group was slightly different from that in the HC group, which decreased rapidly after birth and then kept stable. This is different from the results of some literature works. Wang et al. showed that in the first 2 years after birth, the average CT development of the whole cerebral cortex followed an “inverted U-shaped” trajectory, and CT increased dynamically in the first year but changed slightly in the second year (22). It may be related to genetic, dietary, and environmental factors due to the different sources of the subjects. On the other hand, the average SA development trajectory of both sides of the brain in the GDD group was similar to that in the HC group, which increased rapidly at first after birth, reached a peak at about 23 months, and remained quite stable afterward. It is suggested that the SA expansion pattern of children with global developmental delay is similar to that of normal children.

In addition, from the developmental trajectory map, we can see that the average CT value of both hemispheres in the GDD group is higher than that in the HC group, and the average SA value in the bilateral brain in the GDD group is lower than that in the HC group. The relevant content is further analyzed in the following content.

### GDD and HC show differences in CT

This study found that for the left cerebral hemisphere, except for insula, the lateral orbitofrontal cortex, medial orbitofrontal cortex, caudal anterior cingulate, and rostral anterior cingulate, the CT values of other brain regions in the GDD group were different from those in the HC group. The CT values of the entorhinal and temporal pole in the GDD group were lower than those in the HC group, while the CT values in the other frontal, temporal, parietal, and occipital lobes were higher than those in the HC group. For the right cerebral hemisphere, except insula, temporal pole, caudal anterior cingulate, and rostral anterior cingulate, the CT values of other brain regions in the GDD group were different from those in the HC group, in which the entorhinal CT value in the GDD group was lower than that in the HC group, while the CT values in the other frontal, temporal, parietal and occipital lobes were higher than those in the HC group. Since the global developmental delay may evolve into autism spectrum disorder and hyperactive attention deficit to a certain extent, the author studies a similar mechanism.

The results of this study showed that the CT values of superior frontal, caudal middle frontal, pars-opercularis, pars-orbitalis, and posterior cingulate increased in both hemispheres compared with those of the HC group. The lateral orbitofrontal cortex and medial orbitofrontal cortex also showed an increase



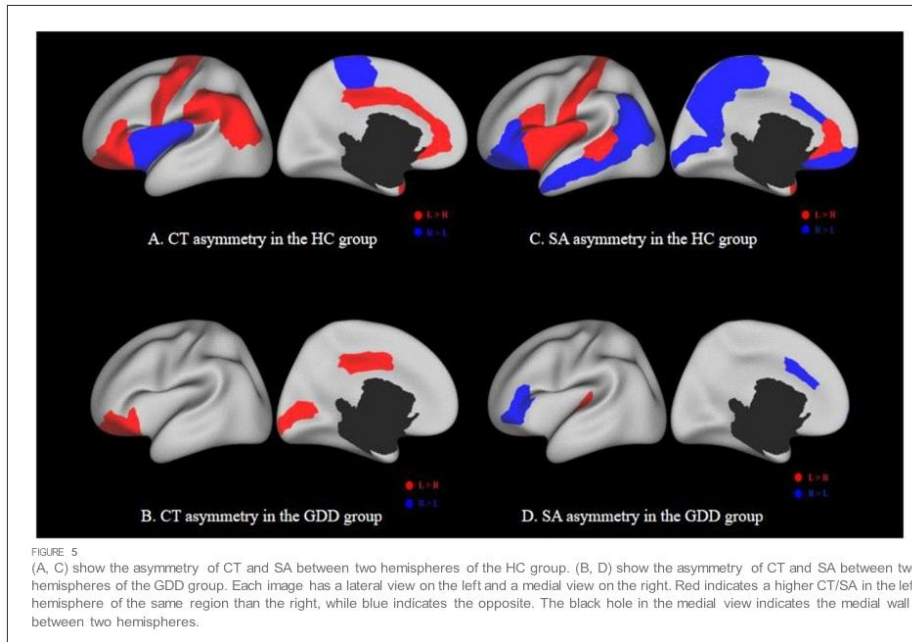


TABLE 3 Brain cortical regions that show significant asymmetry in cortical thickness (CT) in the GDD group.

Brain hemisphere	CT (mm)		P
	Left hemisphere	Right hemisphere	

TABLE 4 Brain cortical regions that show significant asymmetry in cortical surface area (SA) in the GDD group.

Brain hemisphere	SA (mm <sup>2</sup> )		P
	Left hemisphere	Right hemisphere	

Lateral orbitofrontal	4.13	3.87	0.0017*	Pars triangularis	604.62	751.4	0.0174*
Pars orbitalis	4.26	4.08	0.0237*	Pars orbitalis	258.57	349.88	0.0016*
Pericalcarine	3.46	3.31	0.0489*	Frontal pole	114.72	163.92	0.0003*
Posterior cingulate	3.37	3.18	0.0177*	Caudal anterior cingulate	364.02	430.44	0.0327*
Transverse temporal					283.14	208.17	0.0008*

on the right. In van Rooij’s study on autism (23), the same results were observed in the same areas, which may indicate that the children with global developmental delay have the same motor and cognitive control disorder mechanism, resulting in a developmental delay in the corresponding dimension. In Yang et al.’s study, it was found that the thinning of the right superior frontal gyrus was consistent with the typical symptoms of ADHD. These structural abnormalities may correspond to disorders of attention, executive function, and cognitive



control (24). In this study, the increase in CT value of the right superior frontal may indicate that part of the mechanisms between CT and SA, it is not possible to determine which role or the combined effect of the the two causes the corresponding dysfunction.

\* $P < 0.05$ , \*\* $P < 0.01$ .

neurodevelopmental disorder mechanism of motor **GDD and HC show different asymmetry patterns** execution and cognition in children with global developmental delay is opposite to that of ADHD. The asymmetrical areas of the brain in the GDD group were less than those in the HC group. The CT of the In addition, compared with the results of this study, GDD group showed significant left deviation in lateral Kong et al. also found an increase in cortical orbitofrontal, pars-orbitalis, peri-calcarine, and thickness in the right frontal pole, right medial posterior cingulate. The SA of the GDD group showed orbitofrontal gyrus, and right anterior and posterior significant left deviation in transverse temporal and central gyrus in children with Tourette syndrome (25). significant right deviation in pars-triangularis, pars-The frontal pole and medial orbitofrontal cortex orbitalis, frontal pole, and caudal anterior cingulate.

belong to the prefrontal cortex, which is related to the Normal children show obvious left deviation in the thinking and execution of the brain, while the early stage of infants (35), but in this study, the precentral gyrus and postcentral gyrus belong to the number of lateral brain areas in the GDD group is less sensorimotor cortex. The increased cortical thickness in these areas may indicate that the underdevelopment, indicating that there may be neurons in these areas are structurally dense and can maturation disorders in the corresponding brain increase the ability to regulate convulsions (21). These regions. Asymmetry between the left and right findings may show a compensatory effect, but it may hemispheres is an important aspect of human brain also be due to the inhibition of exercise and other tissue, which may be changed under various abilities caused by a too thick CT, which needs further neurodevelopmental abnormalities (35).

study. The left hemisphere responsible for language

The upper parietal lobe is part of the default specialization is one of the earliest observed brain mode network. The default mode network has a asymmetries. Some aspects of language generation functional connection to the caudate nucleus and syntactic processing are then mainly located in through dopamine projection. The striatal the triangle and operculum of the inferior frontal dopaminergic circuit may regulate cognition and gyrus (36). The results of this study show that the left emotion by regulating this network. In this study, it tilting areas of CT and SA in the whole frontal lobe, was found that the CT value of the bilateral parietal including the inferior frontal gyrus, are fewer than lobe was higher than that of the HC group, which may those in the HC group, indicating that the decrease in cause cognitive impairment in children with global lateralization may lead to the corresponding language developmental delay. This is similar to the related development delay. Glasser's neurography analysis results of Zhang et al. on depression (26). using diffusion imaging data showed that the arcuate

This study found that CT increased and SA bundle connecting the superior temporal gyrus (STG) decreased in the bilateral temporal lobe and and the middle temporal gyrus (MTG) to the inferior fusiform, which may cause the disturbance of frontal lobe was asymmetrical to the left, and the left social perception. Adolphs believes that the higher STG and MTG pathways were involved in speech sensory cortex, such as the fusiform gyrus and processing and lexical-semantic processing, superior temporal sulcus, is involved in detailed respectively sensory processing (27). Zilbovicius's study of autism (37). This left deviation was significantly reflected in spectrum disorders has also shown that the the CT hemispheric asymmetry of middle temporal in superior temporal sulcus is a major participant in the HC group, but not in the GDD group. It is further social perception (28). In the study of ADHD, proved that the language cortex of the left Hoogman et al. found that the surface area of hemisphere may not be fully activated, which is children with ADHD was lower, mainly in the related to the underdevelopment of language in frontal lobe, cingulate gyrus, and temporal lobe, children.

and the thickness of the fusiform gyrus and Li et al. showed the leftward asymmetries in the temporal pole cortex was also lower (29). However, medial prefrontal, paracentral, and anterior cingulate this study is contrary to the results in terms of cortices, which expanded substantially during the cortical thickness. Due to the differences in cellular first 2 years of normal infants (38). In this study, we



have not seen the leftward asymmetries in the same regions. Postema et al. showed that ASD was significantly associated with alterations of cortical thickness asymmetry mostly in the medial frontal, orbitofrontal, cingulate, and inferior temporal areas, and also with asymmetry of the orbitofrontal surface area (39). This study does not show the same results. This may indicate that children with GDD have a disorder in the lateralization of the relevant cortex, but also avoid the risk of ASD to a certain extent. Some studies have shown that children with attention deficits have consistent functional disorders in the right inferior frontal gyrus and anterior cingulate cortex (40, 41). The results of this study showed that the lateralization of the corresponding areas in the GDD group was normal, and the thickness of the bilateral anterior cingulate cortex was not different from that in the HC group, indicating that the GDD group may not have cortical dysfunction in the corresponding regions.

### Conclusion

The results of this study show that compared with normal developmental children, the whole brain average developmental trajectory of GDD infants is similar to that of HC infants, but there is an increase in CT and a decrease in SA in many brain regions on both sides of the brain. There may be no correlation between the two aspects, and the specific pathophysiological mechanism needs to be further studied.

The results of this study are helpful for further analyzing the mechanism of neurodevelopmental disorders in children with GDD, providing visual imaging data for clinical diagnosis and treatment, prognosis evaluation, efficacy evaluation and correlation analysis with clinical score, and facilitating further research work related to infant brain development.

### Limitation

Because our sample size is limited, there is no grouping according to etiology and backwardness dimensions, so the final result can only be an overall difference. Next, we will expand the sample size, take etiology and other factors into correlation considerations, and study the specific mechanisms of neurodevelopmental disorders in different dimensions of developmental backwardness.

### Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, eISSN1303-5150

further inquiries can be directed to the corresponding author/s.

### Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

### Author contributions

H-mS: project guidance, data collection and analysis, and article writing and modification. Q-yL: project implementation, data collection and analysis, and article writing and revision. RX: data post-processing, statistical analysis, and article modification. Z-dZ and J-xW: clinical data collection. X-yY: interpretation of results. JY, BJ, and Y-jW: image data collection. HY: image examination and scanning. FW: project guidance, data post-processing, and article modification. All authors contributed to the article and approved the submitted version.

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### Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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