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A preliminary study of cortical morphology changes in acute brainstem ischemic stroke patients

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Abstract

The study aimed to explore the cortical thickness and gyrification abnormalities in acute brainstem ischemic patients in both the ipsilateral and contralateral hemisphere compared with healthy controls. Structural magnetic resonance imaging data were prospectively acquired in 48 acute brainstem ischemic patients, 21 patients with left lesion and 27 with right lesion, respectively. Thirty healthy controls were recruited. Cortical morphometry based on surface-based data analysis driven by CAT12 toolbox implemented in SPM12 was used to compare changes in cortical thickness and gyrification. Significant decreases of cortical thickness loss were found in bilateral cerebral hemispheres of the brainstem ischemic patients compared to the healthy controls ($P < .05$, family-wise error (FWE)-corrected). We also found significant gyrification decreases in the insula, transverse temporal, supramarginal of the ipsilateral on hemisphere in the right brainstem ischemic patients compared to the healthy controls ($P < .05$, FWE-corrected). Brainstem ischemic patients have widely morphological changes in the early phase and may be helpful in designing individualized rehabilitative strategies for these patients.

Abbreviations: 3D-TFE = 3-dimensional turbo fast echo, ANOVA = analysis of variance, CSF = cerebrospinal fluid, DTI = diffusion tensor imaging, FA = flip angle, FOV = field of view, FWE = family-wise error, GM = gray matter, MRI = magnetic resonance imaging, TE = echo time, TR = repetition time, VBM = voxel-based morphometry, WM = white matter.

Keywords: brainstem stroke, cortical thickness, gyrification

1. Introduction

Ischemic brainstem strokes constitute 10% of all ischemic brain stroke.[1] Posterior circulation stroke has traditionally been considered with high morbidity and mortality.[2] Associated symptomatology includes vertigo, cranial nerve symptoms, and crossed or uncrossed corticospinal tract findings.[1]

It is well known that structural damage and reorganization can occur in brain regions outside of the lesion in patients with stroke.[3,4] Previous study had demonstrated that brainstem stroke patients had functional changes in the default-mode network and sensorimotor network than healthy controls in the early chronic phase.[5] Recently, an increasing number of imaging studies focused on the gray matter (GM) and white matter (WM) structural changes in stroke patients.[6–8] Stroke can injure WM tracts directly and lead wallerian degeneration. Diffusion tensor imaging (DTI) provides measures associated with WM microstructural properties.[6] For detecting GM structural changes, most of the studies used voxel-based morphometry (VBM) analysis of brain structure, which focused on volume differences.[4] Dang et al quantified changes of GM volume in acute subcortical infarct patients and they found GM volumes decreased significantly in diffuse areas including the ipsilateral supplementary motor area and the contralateral insula.[3] Recently, Jiang et al also found that both the capsular stroke and pontine stroke in chronic phase showed widely GM volume decrease.[8] Nowadays, different approaches have been extensively used as tools to measure specific morphometric variables of the cortex including cortical thickness, surface area, cortical volume, complexity and gyrification.[9,10] These metrics have proven to be powerful to evaluate differences or abnormalities in the brain structure in lots of disorders.[11–13] Cortical thickness is a key biomarker in the diagnosis and prognostication of neurodegenerative disease. Cortical thinning in critical brain regions has been shown a correlation with disease severity and progression in neurodegenerative disease.[14,15] The thickness of

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the cortex can be a useful measure for understanding disease progression and identifying related brain regions.[16] Gyrification analysis offers a novel approach to analysis brain structure since it targets morphometric properties, which are not captured by VBM or cortical thickness analyses.[17]

In the present study, we used a surface-based morphometric analysis of cortical thickness and gyrification based on the absolute mean curvature approach to test whether the acute brainstem stroke is associated with some brain areas changes in cortical thickness and gyrification.

2. Materials and methods

2.1. Subjects and clinical data

All subjects provided written informed consent before their participation in the study protocol, which was approved by the Research Ethics Committee of the Nanjing Medical University.

All brainstem ischemic participants were recruited at the department of neurology in our hospital from January 2018 to April 2019. Finally, 21 left brainstem ischemic patients and 27 right brainstem ischemic patients were obtained. The inclusion criteria for patients were as follows: (1) between 40 and 70 years of age; (2) right-handedness; (3) first-onset ischemic stroke; (4) the time of examination was within 3 days after the onset. Exclusion criteria for all subjects were as follows: (a) a contraindication for magnetic resonance imaging (MRI); (b) severe quadriplegia; (c) a history of neurological and psychiatric disorders; (d) severe WM hyperintensity manifesting as a Fazekas scale score >1 dehydration; (e) a history of medication; (f) thyroid function, liver function, renal function, electrolytes abnormal. In addition, 30 healthy controls were recruited through online advertisements (aged between 40 and 70 years, all right-handed and completed at least 6 years of education). The groups were matched for age, gender, and education.

2.2. MRI acquisition

MRI data were acquired using a 3.0 Tesla MRI scanner (Ingenia, Philips Medical Systems, Netherlands) with an 8-channel receiver array head coil and parallel imaging was employed. Head motion and scanner noise were alleviated using foam padding and earplugs. Subjects were instructed to lie quietly and avoid any head motion during the scan. Structural images were acquired with a 3-dimensional turbo fast echo (3D-TFE) T1WI sequence with high resolution as follows: repetition time (TR) = 8.1 ms; echo time (TE) = 3.7 ms; slices = 170; thickness = 1 mm; gap = 0 mm; flip angle (FA) = 8°; acquisition matrix = 256 × 256; field of view (FOV) = 256 mm × 256 mm. The structural sequence was obtained in 5 min and 29 s.

2.3. Data analysis

For surface-based morphometry (SBM), we used the Statistical Parametric Mapping analysis package (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) together with the Computational Anatomy Toolbox for SPM (CAT12, http://www.neuro.uni-jena.de/cat/) measuring cortical thickness and gyrification. Cortical thickness and the central surface were calculated in 1 step specified in Dahnke et al.[18] All images underwent automated segmentation to GM, WM, and cerebrospinal fluid (CSF); affine registration to an MNI template space. The gyrification can be extracted based on an absolute mean curvature approach. Central cortical surfaces were created for both hemispheres separately. Finally, all surface measures were resampled and smoothed with a Full Width at Half Maximum (FWHM) Gaussian kernel of 15 mm.

2.4. Statistical analyses

Differences in demographics between patients with stroke and healthy controls were assessed using 1-way analysis of variance (ANOVA) for continuous variables and a χ^2 test for proportions by the SPSS 19.0 software package (SPSS, Inc., Chicago, IL, USA). Statistical significance was set to $P < .05$.

The cortical thickness and gyrification of the left and right hemispheres were separately statistically analyzed using 2 sample t tests corrected for age, sex, years of education, total intracranial volume (TIV), systolic and diastolic blood pressure. Correction for multiple comparisons was performed using the cluster-level family-wise error (FWE) method, resulting in a cluster defining threshold of a P value equal to .001 and a corrected cluster significance of a P value <.05.

3. Results

3.1. Demographic and clinical characteristics

The characteristics of patients with pontine stroke patients, basal ganglia stroke patients and healthy subjects were summarized in Table 1. The 3 groups were well-matched with age, gender and education. There was no significant difference on NHISS between the left brainstem stroke patients and the right brainstem stroke patients ($P > .05$). And, there was no significant difference on diabetes, smoke, alcohol between the 3 groups (all $P > .05$). The healthy controls had the least number of hypertensive patients ($P < .001$).

3.2. Cortical thickness and gyrification

We found significant decreases of the cortical thickness in both hemispheres of the brainstem ischemic patients compared to the healthy controls ($P < .05$, FWE corrected). Figures 1 and 2 showed the location of these clusters on the cortical thickness of the left and right brainstem ischemic patients respectively. Tables 2 and 3 listed the detailed information of these clusters. In the ipsilateral hemisphere, the left brainstem ischemic patients showed lower cortical thickness in insula, superior temporal, superior frontal, caudal anterior cingulate, postcentral, precentral, parahippocampal, fusiform, entorhinal. While the right brainstem ischemic patients showed lower cortical thickness in insula, superior temporal, transverse temporal, superior frontal, caudal anterior cingulate, posterior cingulate, pars opercularis, pars triangularis, precentral, medial orbitofrontal and rostral middle frontal. In addition, there also existed some cortical thickness decrease in the contralateral hemisphere. In the left brainstem ischemic patients, the clusters concentrated on the superior temporal, insula, transverse temporal, superior frontal, caudal anterior cingulate, pars opercularis, pars triangularis and precentral. Furthermore, the right brainstem ischemic patients showed cortical thickness decrease in the contralateral hemisphere of insula, transverse temporal, pars triangularis, pars opercularis, pars orbitalis, lateral orbitofrontal, precentral and postcentral.

We also found significant gyrification decreases in the insula, transverse temporal, supramarginal of the ipsilateral hemisphere

Table 1

Demograpic and clinical characteristics of all subjects.

	Left (n=21)	Right (n=27)	Healthy controls (n=30)	*P*
Age (yr)	59.57±8.58	64.00±7.71	59.87±5.59	.053
Gender (male/female)	14/7	15/12	17/13	.701
Education (yr)	8.44±1.80	7.81±1.63	7.77±1.91	.310
NHISS	3.77±1.98	3.74±2.56	–	.931
TIV	1431.90±151.30	1343.56±108.16	1396.70±129.15	.062
Hypertension (%)	18 (86)	22 (81)	13 (43)	.000
Systolic pressure	143.76±8.93	142.07±9.11	133.67±12.52	.001
diastolic pressure	79.67±7.08	80.93±7.64	77.10±6.99	.134
Diabetes (%)	12 (57)	17 (63)	14 (47)	.455
Smoke (%)	7 (33)	6 (22)	5 (17)	.387
Alcohol (%)	6 (29)	7 (26)	12 (40)	.487
Symptoms				
Speaking difficulty	2	3	–	.461
Swallowing difficulty	5	7	–	.252
Limbs weakness	12	15	–	.912
Sensation loss	3	3	–	.741

TIV = total intracranial volume.

in the right brainstem ischemic patients compared to the healthy controls (Fig. 3; Table 4). However, significant differences in gyrification between the left brainstem ischemic patients and healthy controls were not found.

4. Discussion

In the current study, cortical morphometry based on CAT12 was applied to quantify cortical thickness and gyrification in the acute brainstem ischemic patients compared to healthy controls. Abnormal changes in cortical thickness were observed in the brainstem ischemic patients in bilateral cerebral hemispheres. In addition, we also detected gyrification decreases in the insula, transverse temporal, and supramarginal of the ipsilateral hemisphere in the right brainstem ischemic patients. This indicates that damage do not only affect the lesion territory but also sites distant from the injury after the brainstem ischemic.

In this study, we found the brainstem ischemic patients had a cortical thickness decrease in both the ipsilateral and contralateral hemisphere of the insula and the ipsilateral hemisphere of the anterior cingulate cortex. Unlike other neurodegenerative diseases, for example, Parkinson's disease usually showed reduced thickness in anterior cingulate cortex and posterior cingulate cortex[19] and Alzheimer's disease exhibited a cortical thickness decrease in hippocampus,[20] the brainstem stroke patients showed a cortical thickness decrease typically in the insula. Fischer et al identified and characterized a human brain network derived from coma-causing brainstem lesions and they found that a small region in the pontine was functionally connected to the insula and anterior cingulate cortex.[21] This demonstrated that there did exist a connectivity network between these areas. Hence, the brainstem damage may lead structure changes of the insula and anterior cingulate cortex. In addition, the anterior cingulate cortex is one of the prefrontal limbic

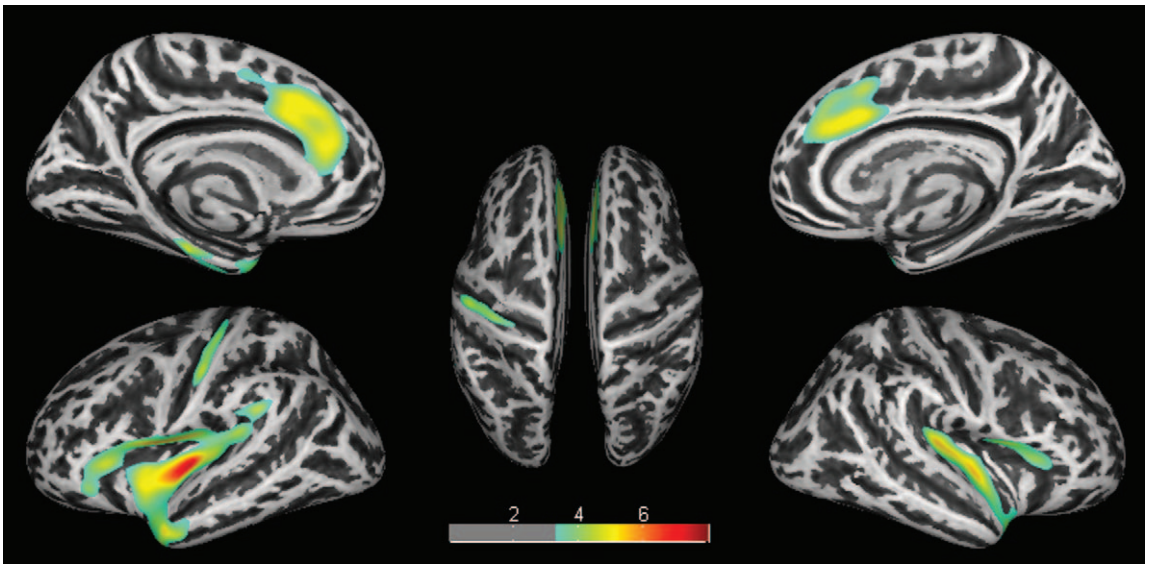

Figure 1. Significant cortical thinning in left brainstem stroke patients compared to the healthy controls.

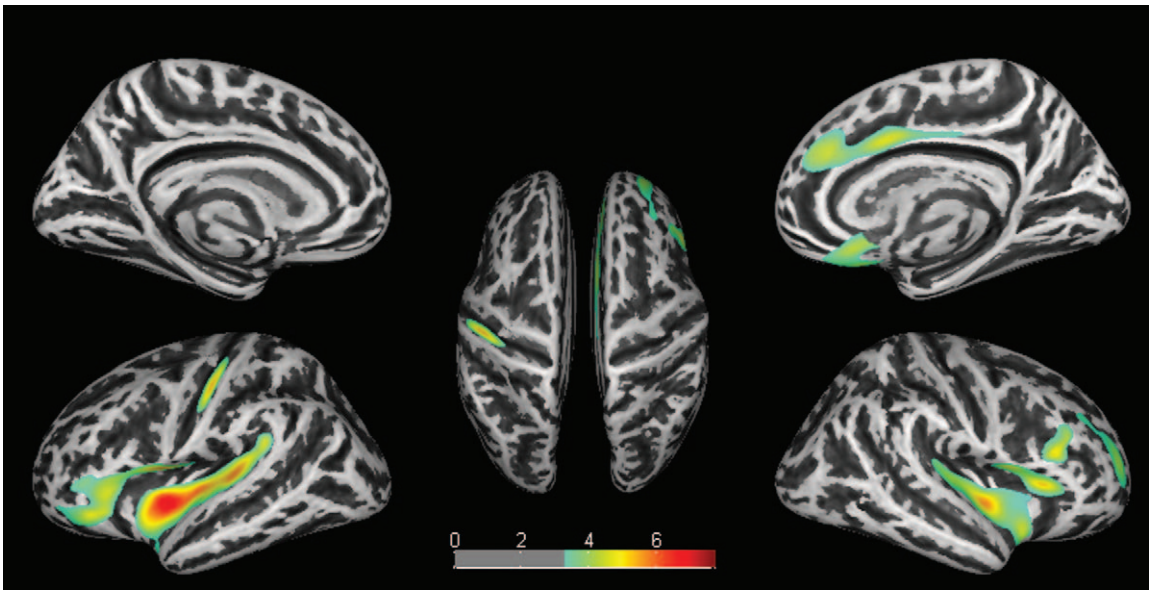

Figure 2. Significant cortical thinning in right brainstem stroke patients compared to the healthy controls.

structures central to the integration of affective, sensory, and cognitive processes.[22] Therefore, the brainstem ischemic patients usually have a bad outcome.

The brainstem ischemic stroke patients also showed widely cortical thickness decrease in the frontal lobe. The precentral gyrus is the anatomical location of the primary motor cortex, which is responsible for controlling voluntary motor movement on the body's contralateral side.[23] Due to the significant role in motor movements, the precentral gyrus is the initiating point for several motor pathways, including, the corticospinal tract, the corticobulbar tract, and the cortico-rubrospinal tract.[24] Consistent with prior study, the precentral gyrus can also be affected by the brainstem stroke.[25] Broca's area, which includes the pars triangularis and pars opercularis, is a neuroanatomic region important in speech-language production.[26] Recently, Pani et al found that the fractional anisotropy values of pars opercularis can predict post-stroke speech fluency.[27] The left and right brainstem ischemic patients both shows pars opercularis and pars triangularis cortical thickness decrease, this may be a possible explanation to the dysarthria and aphasia symptoms.

The superior temporal gyrus and middle temporal gyrus is key areas correlated to auditory.[28] Luo et al found that the silent cerebral infarction patients showed GM volum reduced in superior temporal gyrus and middle temporal gyrus.[29] Therefore, abnormal cortical thickness decrease in the superior temporal gyrus and the middle temporal gyrus may be related to the dysfunction of auditory in the brainstem ischemic patients.

Cortical gyrification is a dynamic process that increases with cortical surface area and decreases with age.[15,30] It has been proved that gyrification can be a useful index to investigate structure-cognition relationships.[9] The most prominent gyrification decreases in our study was observed in the insula,

Table 2

Clusters showing higher rate of cortical thinning in the left brainstem stroke patients compared to the healthy controls.

Hemisphere	Cluster size	*T*	Overlap	Region
Ipsilateral	12703	7.2	24%	Insula
			19%	Superior temporal
	2763	5.1	59%	Superior frontal
			33%	Caudal anterior cingulate
	1481	4.6	86%	Postcentral
			14%	Precentral
	973	4.7	58%	Parahippocampal
			21%	Fusiform
			20%	Entorhinal
Contralateral	4601	5.4	39%	Superior temporal
			34%	Insula
			14%	Transverse temporal
	2668	5.2	70%	Superior frontal
			29%	Caudal anterior cingulate
	1293	4.6	48%	Pars opercularis
			27%	Pars triangularis
			22%	Precentral

Table 3

Clusters showing higher rate of cortical thinning in the right brainstem stroke patients compared to the healthy controls.

Hemisphere	Cluster size	*T*	Overlap	Region
Ipsilateral	4137	5.6	60%	Insula
			24%	Superior temporal
			15%	Transverse temporal
	2188	4.5	42%	Superior frontal
			37%	Caudal anterior cingulate
			21%	Posterior cingulate
	1680	5.1	42%	Pars opercularis
			32%	Pars triangularis
			19%	Precentral
	1143	4.2	84%	Medial orbitofrontal
	903	4.3	100%	Rostral middle frontal
Contralateral	6027	7	40%	Superior temporal
			34%	Insula
			17%	Transverse temporal
	4098	5.4	35%	Pars triangularis
			20%	Pars opercularis
			16%	Pars orbitalis
			13%	Lateral orbitofrontal
			13%	Precentral
	1117	5.2	89%	Postcentral

transverse temporal, supramarginal of the ipsilateral hemisphere in the right brainstem ischemic patients. Insular cortex, which serves to identify salient stimuli from the environment and to initiate cognitive control signals to guide behavior.[31] The result may indicate that the brainstem ischemic patient may have a cognitive impair. The transverse temporal gyrus located in the area of primary auditory cortex is responsible for processing auditory perception and language preprocessing.[32] The cortical thickness and gyrification both decrease in the right brainstem ischemic patients indicate that the patient may have an auditory dysfunction than the other location. Ben-Shabat et al found the right supramarginal gyrus and dorsal premotor cortices were involved in the coding of proprioceptive information at the wrist in controls, and showed decreased task-related activation in the subjects with stroke.[33] Consistently, the brainstem ischemic patients also showed a structure change of the supramarginal.

Our study has some limitations. Firstly, our results are cross-sectional and future work in longitudinal studies to study the dynamic change of the cortical morphology is required. Secondly, we only study the cortical morphology of cortical thickness and gyrification, future studies should be performed to explore the other cortical morphology like surface area, cortical volume, and complexity of the cortex. Finally, we did not perform any cognitive tests. Further studies employing cognitive tests should be conducted to better elucidate the relationship between disrupted morphology changes and cognitive dysfunction.

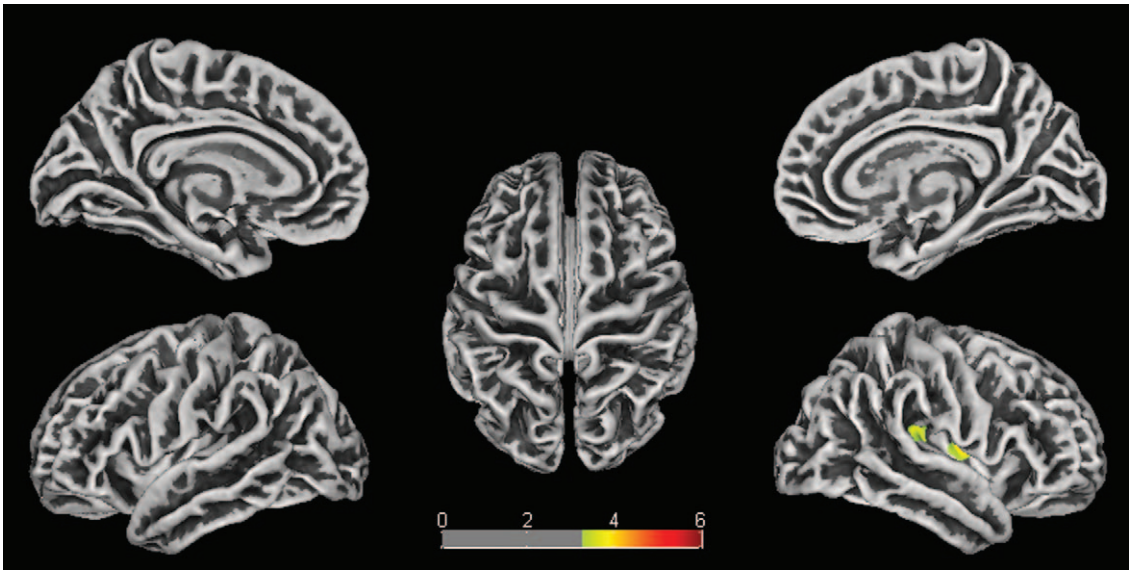

Figure 3. Significant cortical gyrification decrease in right brainstem stroke patients compared to the healthy controls.

Table 4

Clusters showing higher rate of cortical gyrification decrease in the right brainstem stroke patients compared to the healthy controls.

Hemisphere	Cluster size	*T*	Overlap	Region
Ipsilateral	1030	5.5	91%	Insula
	980	3.8	21%	Transverse temporal
			21%	Supramarginal

5. Conclusion

Brainstem ischemic patients have widely morphological changes in the early phase and may be helpful for designing individualized rehabilitative strategies for these patients.

Author contributions

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Visualization: Wen Geng.
Writing – original draft: Huiyou Chen, Mengye Shi.
Writing – review & editing: Xindao Yin, Yu-Chen Chen.

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