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ORIGINAL RESEARCH

Clinical Features, Brain-Structure Changes, and Cognitive Impairment in Basal Ganglia Infarcts: A Pilot Study

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Introduction: Stroke has been considered to raise the risk of dementia in several studies, but the relationship between brain structural changes and poststroke cognitive impairment (PSCI) is unclear.

Methods: In this study, 23 PSCI patients with basal ganglia infarcts after 2 weeks and 29 age-matched controls underwent magnetic resonance imaging measuring cortical thickness and volume changes, as well as neuropsychological tests. CI was derived from a performance score <1.5 standard deviations for normally distributed scores. We compared *Z* scores in different cognitive domains and cortical thickness and volumes in two groups. Multiple linear regressions were used to investigate the relationship between cortical thickness and volumes and neuropsychological tests.

Results: A majority of PSCI patients were in their 50s (55.19±8.52 years). PSCI patients exhibited significantly decreased *Z* scores in multiple domains, such as memory, language, visuomotor speed, and attention/executive function. The volumes of the middle posterior corpus callosum, middle anterior corpus callosum, and hippocampus in PSCI patients were markedly lower than controls. The thickness of the right inferior temporal cortex and insula were significantly smaller than controls. It found that the reduced right hippocampus was related to executive dysfunction. Hippocampus dysfunction may be involved in language impairment ($p<0.05$) in PSCI patients with basal ganglia infarcts.

Conclusion: These findings demonstrated that brain structure changed after ischemic stroke, and different gray-matter structural changes could lead to specific cognitive decline in PSCI patients with basal ganglia infarcts. Atrophy of the right hippocampus potentially serves as an imaging marker of early executive function of PSCI.

Keywords: hippocampus volume, poststroke cognitive impairment, structural changes

Introduction

Poststroke cognitive impairment (PSCI) is frequent, carries a poor prognosis, and remains underdiagnosed. Our previous study showed that it could affect up to 59% of stroke patients and that half the cases might develop dementia.[1] Stroke patients with basal ganglia infarct may have good physical recovery, but usually suffer long-term CI. The most impacted cognitive domains after stroke are executive functions/attention and memory, which are mostly related to stroke severity and territory.[2] The prevalence of memory impairment is 23%–55% at 3 months.[3] The human memory system can be classified into long-term memory and short-term memory and various brain regions involved in memory processes, including the medial temporal lobe (eg, hippocampus), prefrontal cortex, inferior and lateral temporal lobes, basal ganglia, and cerebellum.[2,4]

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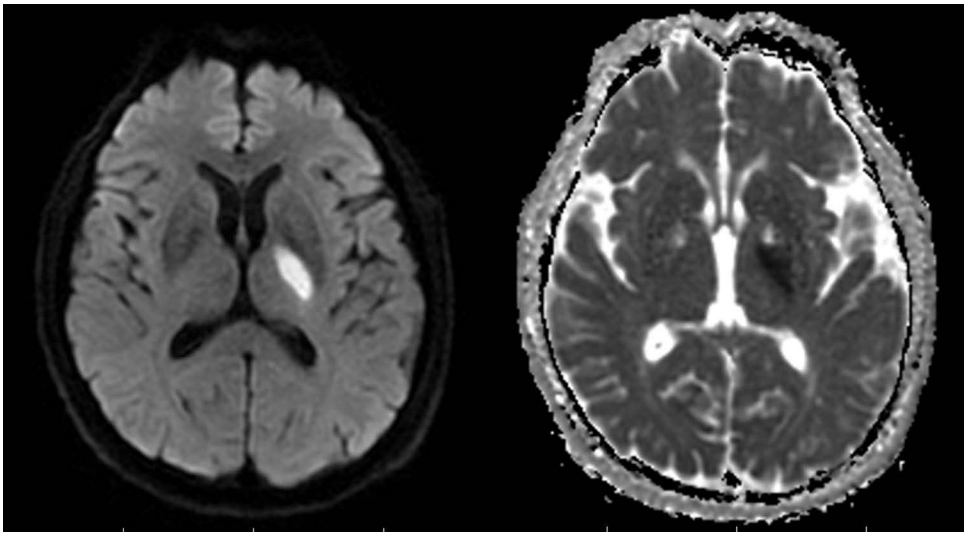

Figure 1 MRI of a new infarction in basal ganglia regions.

Basal ganglia serve as a basic unit of complicated cognitive tasks.[5,6] The basal ganglia region is rich in blood supply and is vulnerable to infarction or ischemic injury. Stroke in the basal ganglia is associated with the dysfunction of executive/attention, memory, learning and visuospatial skills[7] (Figure 1). Despite this connection between basal ganglia infarction and CI,[8] its underlying neural mechanism remains unclear. One study reported that this cognitive decline was primarily related to the dysfunction of cortico–basal ganglia–thalamocortical loops.[9] Furthermore, basal ganglia injury may lead to dysfunction of other cortical regions and functional networks. Stroke with basal ganglia might result in complex functional impairments not constrained to just local functional abnormalities.[10] Another study demonstrated that CI after basal ganglia stroke resulted not only from the site of direct ischemia or infarction but also from the functional abnormalities of distant functionally connected areas.[11] Basal ganglia stroke might lead to the dysfunction of the default-mode network, which is one of the important networks involved in cognition. Basal ganglia infarction might disrupt the basal ganglia–cortex circuits and lead to impairment of multifunctional networks in the whole brain, and is associated with CI.[12]

Many studies on the relationship between structural MRI and cognition have focused on hippocampal volume in mild CI (MCI) and Alzheimer's disease.[13] Hippocampal atrophy is also associated with poststroke dementia.[14] Other studies showed prominent volume reduction in the temporal lobes, as well as subregions in temporal lobes in MCI patients, such as inferior, medial, and posterior temporal gyrus, temporal pole, and parahippocampus.[15] Studies exploring the link between brain-structure changes and the development of PSCI have shown inconsistent results. However, in these studies, cognitive evaluation was evaluated using the Montreal Cognitive Assessment (MoCA) test.[16] One study that included patients with lacunar stroke in basal ganglia showed significant CI.[17] Perivascular spaces of the basal ganglia in community-dwelling individuals free of stroke and dementia can lead to dementia over a long period.[18] The different cognitive domains after an ischemic stroke and their relationship with structural MRI changes remain less clear. Most studies have focused on cognitive function of stroke patients in the chronic phase. There are few studies that have investigated cognition after stroke with basal ganglia infarcts in the acute phase. The goal of this study, therefore, was to investigate changes in cortical thickness and volume in PSCI patients with basal ganglia infarcts at 2 weeks compared to healthy controls and to evaluate the relationship between distinct structural changes and CI.

Methods

PSCI Patients

A total of 23 mild ischemic stroke patients were enrolled, as well as 29 healthy controls with age, sex, and education matched. All the patients were first-ever stroke and recruited consecutively from the Department of Neurology, Beijing Tiantan Hospital at Capital Medical University between August 2015 and November 2016. The study population

comprised patients with an ischemic stroke within 7 days, with infarction of basal ganglia regions, with first-ever stroke, with National Institute of Health Stroke Scale (NIHSS) score ≤3, aged 35–65 years.

We excluded patients with stroke mimics (ie, seizures, migraine) obvious demylination or silent infarction on MRI, illiteracy, history of psychosis (documented in medical records) or major depression on the Hamilton Depression Rating Scale (HDRS; score ≥17), delirium and preexisting dementia on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; score >3.38),[19] and other factors that interfere with cognitive evaluation, eg, severe aphasia defined as NIHSS item 9 >2, consciousness disorders defined as NIHSS item 1a>1 or 1b>1, hearing or visual impairment, severe unilateral neglect, or dyslexia.

Of the 90 consecutive patients with basal ganglia stroke recruited, 50 were excluded. The reasons for exclusion were NIHSS score >3 (n=14), not first stroke (n=12), contraindications to MRI or dropout during MRI (n=8), severe aphasia or dysarthria (n=10), severe hearing impairment (n=4), and illiteracy (n=2). The present analyses included 40 basal ganglia mild-stroke patients. Based on the neurological tests, 23 patients with PSCI were recruited. Fourteen had lesions in the left basal ganglia and nine in the right basal ganglia (Figure 1).

Control Subjects

A total of 29 healthy controls from the community matched for age, sex, and education were selected. The control subjects had no history of neuropsychiatric disorders, myelination, or lacunar infarction on MRI. All procedures were approved by the Beijing Tiantan Hospital Ethics Review Board. Written informed consent was obtained from all participants.

Data Collection and Clinical Assessment

The demographic details of different subjects are presented in Table 1. Basic daily functioning and complex function were assessed by the basic activities of daily living (ADL) scale[20] and instrumental ADL scale,[21] respectively. Depression condition was assessed based on the Hamilton Depression Scale (HDRS).[22] The diameter and locations of lesions were checked by two radiologists.

Cognitive Assessment

Global cognitive function was assessed using the Chinese version of the MoCA scale.[23] One point was added to the MoCA score for those with education <12 years.[24] The neuropsychological test battery examined five cognitive domains (see Table 1), and was completed within 10 (IQR 2) days of admission. The interval between the neuropsychological assessment and MRI scan was 12 hours. The *Z* score was defined as onee that fell within the distribution of scores for controls, and was calculated for the neuropsychological tests. CI was defined as a score of 1.5 standard deviations below the mean on any neuropsychological test of the normative study. Final diagnoses of CI subjects were assigned based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.[25]

Table 1 Cognitive tests for each of the domains assessed

Domain	Task	Index
Memory	Auditory Verbal Learning Test	Total score, delayed recall score
	Rey–Osterrieth Complex Figure Test (RCFT)	Delayed recall score
Language	Animal Fluency Test (AFT)	Total number animals generated
	Boston Naming Test (BNT, 30-item)	Total number correct with no cue
Visuospatial ability	RCFT	Total copy score
Visuomotor speed	Symbol Digit Modality Test (SDMT)	Total number correct
Attention/executive function	Modified Chinese version of Trail Making Test (TMT)-A	Time (s)
	Modified Chinese version of Trail Making Test (TMT)-B	Time (s)
	Modified Chinese version of Stroop Color–Word Test (CWT) — color	Total number correct

Image Acquisition

T_1-weighted images were obtained using a 3 T Prisma device (Siemens Healthcare, Erlangen, Germany). The parameters were TR = 2300 ms, TE = 2.3 ms, TI = 900 ms, scanning field 240×240 mm, matrix 256×256, layer thickness 1 mm, and interlayer spacing 1 mm. The FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu) were used for cortical reconstruction and volumetric segmentation (version 6.0.0). Cortical thickness and volume were quantified. Briefly, this procedure included motion correction, averaging of multiple volumetric T_1-weighted images, non-brain tissue removal, automated Talairach transformation, segmentation of subcortical white-matter and deep gray-matter volumetric structures, intensity normalization, tessellation of the gray-matter and white-matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray matter–white matter and gray matter–cerebrospinal fluid borders at the location where the greatest shift in intensity defined the transition to the other tissue class.

Statistical Analysis

Statistical analyses were conducted with SPSS 20.0. Significance was set at $p<0.05$. Continuous variables are expressed as means ± SD or medians (IQR) according to their distribution (normal or skewed). Discrete variables were compared by X^2 tests. Spearman correlation analyses were performed between the Z score of cognitive function and cortical thickness or volume. We evaluated the association between cognitive function and cortical thickness or volume using further multiple linear analyses adjusted for potential confounders, including average age, years of education, and IADL score.

Results

Characteristics and Clinical Profile of Patients

The PSCI group had significantly less education and higher instrumental ADL scores than the control group ($p<0.05$). There were no significant differences in age, sex, scores on the HDRS, basic ADL, or IQCODE, prevalence of hypertension, diabetes, hyperlipidemia, current or ever drinking, and current or ever smoking between the groups. Median (IQR) NIHSS and Modified Rankin Scale score were 3 (4) and 1 (1), respectively. Most patients had small-artery occlusion (n=19, 82.61%) and three large atherothrombotic infarction (13.04%) strokes. The average diameter of lesions was 17.57±8.81 mm (Table 2).

Table 2 Demographic information for control and PSCI groups

	Control n=29	**PSCI n=23**	***p***
Age (years), mean ± SD	51.11±6.89	55.19±8.52	0.43
Sex (male), n (%)	21.00(72.41)	19.00(82.61)	0.51
Education (years), mean ± SD	11.00±2.49	9.74±1.74	0.045*
NIHSS score at admission, median (IQR)	–	3.00 (4.00)	–
Functional status			
Modified Rankin Scale score, median (IQR)	–	1.00 (1.00)	–
IQCODE score, mean ± SD	3.05±0.09	3.11±0.13	0.052
HDRS score, median (IQR)	3.00 (2.00)	3.00 (2.00)	0.12
Instrumental ADL score, mean ± SD	8.00±0.00	9.32±1.49	<0.001**
Basic ADL score, mean ± SD	6.00±0.00	6.22±0.85	0.23
Diameter of lesion (mm), mean ± SD	–	17.57±8.81	–
Left basal ganglias, n (%)	–	30.00(75.00)	–
Hypertension, n (%)	20.00(68.97)	16.00(69.56)	1.00
Diabetes, n (%)	8.00(27.59)	9.00(39.13)	0.27
Hyperlipidemia, n (%)	12.00(41.38)	10.00(43.48)	1.00
Current or ever drinking, n (%)	21.00(72.41)	15.00(65.21)	0.76
Current or ever smoking, n (%)	21.00(72.41)	14.00(60.87)	0.55

Notes: *$p<0.05$; **$p<0.01$.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; HDRS, Hamilton Depression Rating Scale; ADL, activities of daily living.

Comparison of Neuropsychological Tests

The PSCI group showed significantly lower *Z* scores than the control group in the cognitive domains of memory, visuomotor speed, language, and attention/executive function ($p<0.05$, Table 3 and Figure 2).

Comparison of Cortical Thickness and Brain Volume

The thicknesses of the right inferior temporal cortex and insula in the PSCI group were significantly less than controls ($p<0.05$). The volume of the middle posterior corpus callosum, middle anterior corpus callosum, and hippocampus in PSCI patients was remarkably less than controls ($p<0.05$) (Table 4). There were no significant difference in bilateral volumes of amygdala, caudate, putamen, or pallidum between the control and PSCI groups (Supplemental Table 1).

Correlation Analyses Between Cortical Thickness or Brain Volume and *Z* Scores of Cognitive Scales

Z scores for executive function were significantly and positively correlated with thickness of the right insula cortex ($r=0.298$, $p<0.05$). *Z* scores for executive function were significantly and positively correlated with volumes of the hippocampus (left $r=0.028$, right $r=0.42$; $p<0.05$) and middle posterior corpus callosum ($r=0.533$, $p<0.05$; Table 5). *Z* scores for language were significantly and positively correlated with thickness of the right inferior temporal cortex ($r=0.360$, $p<0.05$), while *Z* scores for language were significantly and positively correlated with volumes of the hippocampus (left $r=0.445$, right $r=0.471$; $p<0.05$) and middle posterior corpus callosum ($r=0.383$, $p<0.05$; Table 5).

Z scores for memory were significantly and positively correlated with volumes of the hippocampus (left $r=0.446$, right $r=0.386$; $p<0.05$), middle posterior corpus callosum, and middle anterior corpus callosum (posterior $r=0.419$, anterior $r=0.338$; $p<0.05$; Table 5). *Z* scores for verbal memory (total AVLT score) were significantly and positively correlated with volumes of the left hippocampus ($r=0.292$, $p<0.05$) and middle posterior corpus callosum ($r=0.403$,

Table 3 Comparison of *Z* scores in every cognitive domain between control and PSCI groups

	Control (n=29)	PSCI (n=23)	*p*
Cognitive domains			
***Z* scores, median (IQR)**			
Memory	0.18(2.75)	−3.42(3.80)	<0.001**
Verbal memory			
Total score of AVLT	0.13(1.27)	−0.69(1.94)	0.005**
AVLT — delayed recall	0.00 (1.52)	−1.00 (2.00)	0.005**
Visual delayed memory			
RCFT — delayed recall	0.00 (1.52)	−1.75(1.58)	<0.001**
Visuospatial ability	−0.50(1.16)	−1.50(2.63)	0.177
RCFT	−0.50(1.16)	−1.50(2.63)	0.177
Language	0.93(3.26)	−1.21(3.54)	<0.001**
BNT	0.38(1.27)	−1.00 (1.83)	<0.001**
AFT	0.25(2.43)	−0.63(1.50)	0.002**
Visuomotor speed	0.20(1.21)	−1.45(1.90)	<0.001**
SDMT	0.20(1.21)	−1.45(1.90)	<0.001**
Attention/executive function	3.69(3.58)	−1.63(5.44)	<0.001**
TMT-A time	0.02(1.29)	−1.14(1.88)	<0.001**
TMT-B time	0.25(1.34)	−1.14(2.56)	<0.001**
CWT-C time	0.21(0.98)	−0.50(2.04)	0.001**

Note: **$p<0.01$.

Abbreviations: AVLT, Auditory Verbal Learning Test; RCFT, Rey–Osterrieth Complex Figure Test; BNT, Boston Naming Test; AFT, Animal Fluency Test; SDMT, Symbol Digit Modalities Test; TMT-A, modified Chinese version of the Trail Making Test; CWT-C, Color–Word Test — Chinese version.

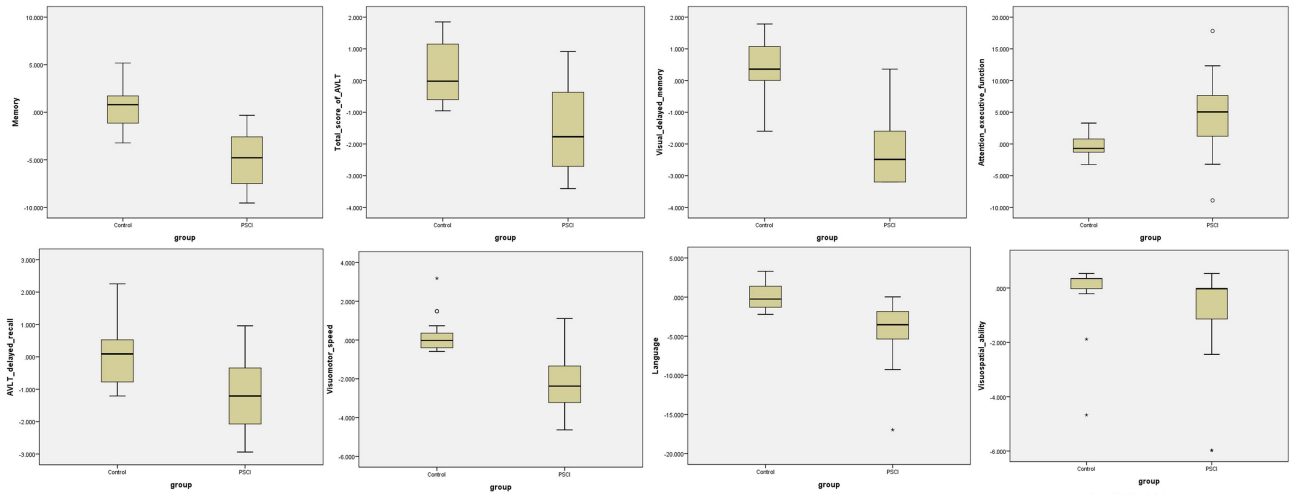

Figure 2 Comparison of neuropsychological tests between control group and PSCI group. *Extreme outliers (>3 times interquartile range); ○mild outliers (>1.5 times interquartile range).

p<0.05; Table 5). Z scores for delayed verbal memory (AVLT delayed recall score) were significantly and positively correlated with volumes of the left hippocampus (r=0.326, p<0.05); and middle posterior corpus callosum (r=0.444, anterior r=0.26; p<0.05; Table 5). Z scores for delayed visual memory (RCFT delayed recall score) were significantly and positively correlated with volumes of the left hippocampus (r=0.36, p<0.05) and middle anterior corpus callosum (r=0.314, p<0.05; Table 5). Z scores for visuomotor speed were significantly and positively correlated with volumes of the hippocampus (left r=0.467, right r=0.432; p<0.05), middle posterior corpus callosum, and middle anterior corpus callosum (posterior r=0.362, anterior r=0.339; p<0.05; Table 5).

Multiple Linear Regression Analyses Between Cognitive Score and Cortical Thickness/Volume

Multiple linear regression analyses indicated that executive function scores (β=0.333, p=0.036) were significantly and negatively correlated with right hippocampus volume after adjustment for age, education, and instrumental ADL score. Language scores were significantly and positively correlated with hippocampus volume after adjustment for age, education, and instrumental ADL score (Table 6).

Table 4 Comparison of cortical thickness and brain volume between control and PSCI groups

	Controls (n=29)	PSCI Group (n=23)	*p*
Cortical thickness of right hemisphere			
Inferior temporal cortex	2.88±0.14	2.78±0.15	0.01*
Insula	3.03±0.15	2.94±0.14	0.01**
Volume of gray matter			
Middle posterior corpus callosum	433.69±65.20	361.40±92.96	0.04*
Middle anterior corpus callosum	486.40±108.90	394.40±95.76	0.02*
Left hemisphere			
Caudate	3453.56±351.61	3869.43±975.70	0.02*
Hippocampus	4427.54±327.84	4084.87±374.19	0.02*
Right hemisphere			
Hippocampus	4720.89± 343.88	4367.49±327.04	0.01**

Notes: *p<0.05; **p<0.01.

Table 5 Spearman correlations between cortical thickness and *Z* scores on cognitive scales

	Right inferior temporal cortex thickness		Right insula thickness		Left hippocampus volume		Right hippocampus volume		Middle posterior corpus callosum volume		Middle anterior corpus callosum volume	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Executive function	0.148	0.310	0.298	0.038*	0.028	0.007**	0.42	0.003**	0.533	<0.001**	0.232	0.109
Language	0.360	0.011*	0.137	0.347	0.445	0.001**	0.471	0.001**	0.383	0.007**	0.252	0.081
Memory	0.191	0.188	0.017	0.905	0.446	0.001**	0.386	0.006**	0.419	0.003**	0.338	0.017*
Total AVLT score	0.198	0.172	0.004	0.981	0.292	0.042*	0.243	0.092	0.403	0.004**	0.250	0.084
AVLT — delayed recall	0.114	0.436	0.031	0.830	0.326	0.022*	0.343	0.016*	0.444	0.001**	0.250	0.084
RCFT — delayed recall	0.224	0.121	0.057	0.697	0.360	0.036*	0.187	0.199	0.255	0.077	0.314	0.028*
Visuomotor speed	0.198	0.173	0.078	0.594	0.467	0.001**	0.432	0.002**	0.362	0.011*	0.339	0.017*

Notes: *$p<0.05$; **$p<0.01$.

Table 6 Multiple linear regression analyses of cortical thickness/volume and related factors

Z score, cognition	Right hippocampus volume			Left hippocampus volume		
	Univariate			Univariate		
	β	*β* (95% CI)	*p*	*β*	*β* (95% CI)	*p*
Executive function	0.333	0.000–0.010	0.036*	0.219	−0.001- 0.008	0.168
Memory	0.283	0.000–0.005	0.055	0.247	0.000–0.004	0.09
Language	0.507	0.001–0.005	0.001**	0.367	0.000–0.004	0.02**

Notes: *$p<0.05$, **$p<0.01$. Adjusted for age, education, and IADL.

Discussion

The current study investigated the characteristics of PSCI patients with basal ganglia infarction. Data showed that PSCI patients exhibited significantly lower *Z* scores in all cognitive domains than controls: including verbal memory, visual memory, visuospatial ability, visuomotor speed, language, and attention/executive function. There is evidence that memory and executive function are affected early in vascular CI.[26] PSCI is also associated with language and visuospatial dysfunction.[27] As for the memory domain, PSCI patients with basal ganglia infarcts have both verbal and visual memory decline. Studies have proved the crucial role of basal ganglia in the verbal memory regulation.[28,29] The functional connectivity of the basal ganglia has been modeled as two second-level modulatory connections that control projections from sensory cortices to the prefrontal cortex and from the hippocampus and medial temporal lobe to the prefrontal cortex.[30] Memory formation includes encoding, storage, and retrieval. A recent study reported that subcortical region dysfunction was related to impaired information retrieval, which could finally lead to visual memory dysfunction.[31] It might explain why patients with basal ganglia infarction exhibited both verbal and visual memory decline.

We explored the brain structural changes and potential mechanism of PSCI with basal ganglia infarcts by measuring cortical thickness and volume. The results showed that the PSCI group had reduced cortical thickness and brain volume across several regions than the control group, such as thickness of inferior temporal cortex and insula cortex and volume of middle posterior corpus callosum, middle anterior corpus callosum, and hippocampus. However, there was no significant difference in volumes of basal ganglia regions, such as the amygdala, caudate, putamen, or pallidum, between the two groups. Our results suggest that brain atrophy is an important substrate for CI in PSCI patients with basal ganglia infarcts. These findings seem to imply that lesions in basal ganglia not only affect local regions but also expand to functionally connected regions. Another study on basal ganglia infarction patients showed altered connectivity of the left inferior temporal gyrus.[12] Cerebral ischemia and reduced cerebral blood flow might disrupt energy metabolism and lead

to metabolic stress. Cells that undergo severe ischemia may die within minutes of the insult or exhibit delayed vulnerability. Cytotoxic edema promotes both a reduction of extracellular volume fraction and changes in membrane permeability.[32] These events eventually damage functions of local regions because of ischemia, but connected regions remotely, because of loss of afferent synaptic input from distally or retrograde axonal degeneration.[33] The hippocampus is rather sensitive to ischemia. It is possible that preexisting hippocampal vulnerability in this study left subjects sensitive to the short-term negative effects of stroke.[34] In multiple linear regression analyses, we found that right hippocampus volume was significantly and positively correlated with executive function. The hippocampus is well known to participate in episodic memory processes. A previous study showed that the hippocampus is associated with subcortical regions and the prefrontal cortex to play an important role in executive functions.[35,36] This functional connectivity and axonal projections enable and enhance learning–behavior translation, and partly explain why hippocampal dysfunctions result in executive deficits. Another study also reported that executive tasks required the coactivation of prefrontal and hippocampal networks.[37] Stroke lesions in basal ganglia might damage the link among the hippocampus, subcortical regions, and the prefrontal cortex and lead to executive dysfunction.

We also find that hippocampus volume was related to language dysfunction. Memory and language share a common neural mechanism. The hippocampus is a part of the language network and contributes to language processing.[38] One structural MRI study showed that hippocampus volume is related to language-processing deficits.[39] Another functional MRI study showed that language rehabilitation is related to enhanced functional connectivity recovery among frontal, temporal, and parietal lobes with the hippocampus.[40] Both support our study findings. Patients with basal ganglia infarcts might have remote structural damage and consequently CIs.

However, this research has several limitations. Firstly, although we selected basal ganglia stroke, it is a challenge to achieve stroke homogeneity in a given sample. Secondly, given the small sample, further research should be done on larger samples to verify the current findings. Thirdly, this study was cross-sectional. The relationship between brain-structure changes and cognition was obtained in the acute phase. We agree that our findings might not be suitable for all stroke patients, especially for those in the chronic phase. We will continue to investigate relationships between brain-structure integrity and cognition at 6 months or 1 year after stroke to determine whether it affects long-term poststroke cognitive function.

This study was conducted firstly to explore the cognitive function of stroke patients with basal ganglia lesions and identify the correlation between brain-structure integrity and cognitive functions in the acute phase. The results suggest that reduced hippocampus volume is associated with language and executive function in stroke patients with basal ganglia at 2 weeks.

Data Sharing

There are no additional data.

Ethics

This trial was reviewed and approved by the Beijing Tiantan Hospital Ethics Review Board (KY-2015-001-01). Written informed consent was obtained from all participants. This study was performed according to the guidelines of Capital Medical University, which abides by the Helsinki Declaration on ethical principles for medical research involving human subjects.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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