Cognitive impairment in two subtypes of a single subcortical infarction

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Abstract

Background: Single subcortical infarction (SSI) is caused by two main etiological subtypes, which are branch atheromatous disease (BAD) and cerebral small vessel disease (CSVD)-related SSI. We applied the Beijing version of the Montreal Cognitive Assessment (MoCA-BJ), the Shape Trail Test (STT), and the Stroop Color and Word Test (SCWT) to investigate the differences in cognitive performance between these two subtypes of SSI.

Methods: Patients with acute SSIs were prospectively enrolled. The differences of MoCA-BJ, STT, and SCWT between the BAD group and CSVD-related SSI group were analyzed. A generalized linear model was used to analyze the associations between SSI patients with different etiological mechanisms and cognitive function. We investigated the correlations between MoCA-BJ, STT, and SCWT using Spearman’s correlation analysis and established cut-off scores for Shape Trail Test A (STT-A) and STT-B to identify cognitive impairment in patients with SSI.

Results: This study enrolled a total of 106 patients, including 49 and 57 patients with BAD and CSVD-related SSI, respectively. The BAD group performances were worse than those of the CSVD-related SSI group for STT-A (83 [60.5–120.0] vs. 68 [49.0–86.5], \(P = 0.01\)), STT-B (204 [151.5–294.5] vs. 153 [126.5–212.5], \(P = 0.015\)), and the number of correct answers on Stroop-C (46 [41–49] vs. 49 [45–50], \(P = 0.035\)). After adjusting for age, years of education, National Institutes of Health Stroke Scale and lesion location, the performance of SSI patients with different etiological mechanisms still differed significantly for STT-A and STT-B.

Conclusions: BAD patients were more likely to perform worse than CSVD-related SSI patients in the domains of language, attention, executive function, and memory. The mechanism of cognitive impairment after BAD remains unclear.

Keywords: BAD; Cognitive impairment; Cerebral small vessel disease; Subcortical infarction; Stroke

Introduction

Cognitive impairment is common after acute stroke.\(^1\) While conceptually this is more likely to occur after large or strategically located areas of cerebral infarction, studies suggest that half of the survivors of first-ever lacunar infarction have cognitive deficits that are severe enough to impair daily activities.\(^2,3\) Underlying cerebral small vessel disease (CSVD) is another pathophysiological explanation, in which domains of executive function, attention, memory, processing speed, and verbal fluency are prominent,\(^4\) yet memory loss is the most commonly impaired cognitive domain after lacunar infarction.\(^5\) While processing speed is one of the earliest and most prominent progressive cognitive impairments associated with CSVD, lesions of the frontal interhemispheric and thalamic projection fiber tracts that involve the frontal-subcortical neuronal circuits are also predictors of processing speed performance in age-related CSVD.\(^6\) Thus, CSVD-related cognitive impairment is likely to depend on lesion location, particularly in the internal capsule, thalamus, caudate nuclei, anterior thalamic radiation, and forceps minor.\(^7\) Through in vivo visualization of proximal culprit plaques in the penetrating arteries of the middle cerebral artery, we propose that branch atheromatous disease (BAD) is a distinct nosological entity of single subcortical infarction (SSI) that may guide management and prognosis.\(^8\) The differences in cognitive performance between the two subtypes of SSIs can be used to distinguish their different etiological mechanisms. The present descriptive investigation compared cognitive performance between patients with different etiological mechanisms.
with BAD (atheromatous plaque of the parent artery at the orifice of the perforating artery) and CSVD-related SSI (lacunar infarction from intrinsic CSVD pathologically characterized by lipohyalinosis and fibrinoid degeneration). Based on the comparison of the differences in the cognitive function of SSI patients with different etiological mechanisms, the correlations between different cognitive function assessment scales in these patients were further analyzed. We also provided reference data for SSI patients using the Shape Trail Test A (STT-A) and STT-B to assess impairment in cognitive function.

Methods

Ethical approval
The study was approved by the Ethics Committee of West China Hospital (No. 2020[324]), and the informed consent was obtained from all participants.

Patients
We prospectively recruited consecutive patients (age, 18–80 years) admitted to West China Hospital between July 2017 and November 2020 with first-ever acute ischemic stroke due to a SSI (basal ganglia, corona radiata, internal capsule, and thalamus) identified by diffusion-weighted imaging (DWI) performed within 14 days of symptom onset. Patients were excluded if they had a history of other neurological or psychiatric diseases or pre-existing cognitive dysfunction; hearing or communication disorder, color blindness, or severe paralysis that would impair performance on tests; evidence of prior stroke on brain imaging; coexistent ≥50% stenosis in any of the ipsilateral internal carotid, middle or anterior cerebral, vertebral, basilar, or posterior cerebral arteries on computed tomography angiography (CTA); multiple lesions on magnetic resonance imaging (MRI) DWI; nonatherosclerotic vasculopathy (e.g., dissection, vasculitis, and moyamoya disease); and evidence of any potential source of cardioembolism (e.g., atrial fibrillation, recent myocardial infarction, dilated cardiomyopathy, valvular heart disease, or infective endocarditis).

Baseline characteristics including age, sex, years of education, dominant hemispheric infarction, lesion location (based on the strategic subcortical infarcts potentially affecting cognitive function in previous studies), cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, current alcohol consumption, and smoking status), and time from symptom onset to admission were systematically recorded. The severity of neurological impairment was measured using the National Institutes of Health Stroke Scale (NIHSS) score. All patients underwent 24 h of electrocardiographic monitoring and/or Holter monitoring and transthoracic echocardiography to exclude those with cardioembolism. The Beijing version of the Montreal Cognitive Assessment (MoCA-BJ), Trail Making Test (TMT), and Stroop Color and Word Test (SCWT) were administered during hospitalization within 14 days after symptom onset. The patients were divided into two groups according to lesion size on DWI: BAD was defined as a SSI lesion (diameter <15 mm) in less than three axial slices.\(^9\)

CSVD MRI markers
Lacunes were defined as round or ovoid lesions (>3 mm and ≤20 mm diameter) occurring in the basal ganglia, internal capsule, centrum semiovale, or brainstem, with cerebrospinal fluid signal intensity on T2 and fluid-attenuated inversion recovery (FLAIR), generally with a hyperintense rim on FLAIR and no increased signal on DWI\(^{10}\) and defined as single or multiple.\(^{11}\) Enlarged perivascular spaces (EPVSs) were defined as small (<3 mm) punctate (if perpendicular) and linear (if longitudinal to the plane of scan) hyperintensities on T2 images in the basal ganglia or centrum semiovale. According to a validated semiquantitative scale of 0 to 4,\(^{12}\) EPVSs in the basal ganglia were categorized as moderate to severe (grades 2–4).\(^{11}\) Deep and periventricular white matter hyperintensities (WMH) were coded from 0 to 3 on the Fazekas scale\(^{13}\) and categorized as either (early) confluent deep (score 2 or 3) or irregular periventricular extending into the deep white matter (score 3).\(^{11}\) Two experienced neurologists blinded to patient data manually assessed the number of lacunes, EPVS, and WMH severity, with 10 patients randomly selected for assessment of the reproducibility of measurements. Any discrepancies between the two observers were resolved by consensus.

Cognitive assessments
The MoCA-BJ was used to assess cognition, as it is a widely accepted, popular, and brief standardized measure of cognition for use after stroke,\(^{14}\) with a cut-off score of 26 showing excellent sensitivity (90.4%) and fair specificity (31.3%) for mild cognitive impairment (MCI).\(^{15}\)

The TMT is another sensitive and popular test used to identify MCI and dementia, with the variant STT for Chinese consisting of two parts\(^{16}\): Part A, in which the participant is asked to connect 25 pre-instructed digits, and Part B, in which the participant is required to alternately connect 25 pre-instructed digits, each appearing twice in both a circle and a square. In practice, derived scores usually remove the speed (in seconds) component from performance to provide a more refined measure of executive control.\(^{17}\) However, Zhao et al.\(^{18}\) developed an index measure, “STT-B-1 min,” defined as the number of correct responses within the first minute, to improve efficiency and performance. Receiver operating characteristic curve (ROC) analysis indicated area under the curve (AUC) values ranging from 0.816 to 0.913 for the STT-A and STT-B, with acceptable sensitivity and specificity.

The SCWT is widely used to evaluate basic human executive functions, particularly attention and informational processes.\(^{18}\) It consists of neutral or incongruent colored words presented to participants who are asked to connect the correct name of a given color (card A, black wording) with the color (card B). Card C features the names of colors but with competing color names (e.g., the word “green” written in red). Scores are derived from the difference in completion times (Stroop interference
were two sided, and statistical significance was set at $P < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM, Armonk, NY, USA).

**Results**

This study enrolled a total of 106 patients, including 49 and 57 patients with BAD and CSVD-related SSI, respectively. CSVD-related SSI patients were more likely to have hypertension and were current smokers, while BAD patients were more likely to have hyperlipidemia and higher baseline NIHSS scores [Table 1]. Table 2 shows the differences in MoCA-BJ, STT, and SCWT tests, with significant differences observed in the STT-A ($r = 0.736$) or Stroop-A (correct) ($r = 0.915$). High correlations were observed between MoCA-BJ and STT and SCWT but not STT B/A ($r = 0.736$) or Stroop-A (correct) ($r = 0.915$), and SIE right numbers ($r = 0.915$). After adjusting for age, years of education, NIHSS, and lesion location, the performance of BAD patients on STT-A and STT-B remained worse than that of CSVD-related SSI patients (STT-A: $\beta$ coefficient, $-16.168$, 95% confidence interval [CI], $-29.363$ to $-2.972$, $P = 0.016$; STT-B: $\beta$ coefficient, $-23.347$, 95% CI, $-43.841$ to $-2.853$, $P = 0.026$) [Table 3].

The results of correlation analysis showed significant correlations between MoCA-BJ and STT and SCWT but not STT B/A ($r = -0.033$, $P = 0.736$); between STT-A and SCWT but not Stroop-A (correct) ($r = -0.053$, $P = 0.593$); between STT-B and SCWT but not STT B/A ($r = -0.022$, $P = 0.823$) or Stroop-A (correct) ($r = -0.183$, $P = 0.061$); and between Stroop-C (correct) and STT but not STT B/A ($r = -0.010$, $P = 0.915$). High correlations were observed for MoCA-BJ and STT-B ($r = -0.640$, $P < 0.001$) [Table 4].

Table 5 shows the optimum performance for STT-A and STT-B in identifying cognitive impairment in patients with...
The results of our study showed that cognitive performance after BAD was significantly worse than that after CSVD-related SSI. We found significant differences in STT-A and STT-B between the groups but not the MoCA-BJ between the groups, which likely reflects its insensitivity to higher levels of cognitive function. These data provide insights into the mechanisms of cognitive impairment after SSI.

### Discussion

The STT is based on the TMT, which was developed for people who speak Chinese as their first language. The test assesses both "rapid visual search" and "visuospatial scanning." Our results indicate that BAD patients exhibit poorer cognitive performance compared to CSVD-related SSI patients. This difference is most pronounced in the STT-A and STT-B tasks, suggesting that BAD has a more profound impact on these cognitive functions.

### Table 2: Baseline differences in cognitive measures between BAD and CSVD-related SSI groups.

| Characteristics          | BAD (n = 49) | CSVD-related SSI (n = 57) | P value |
|--------------------------|-------------|--------------------------|---------|
| MoCA score <26           | 33 (67.3)   | 32 (56.1)                | 0.238   |
| MoCA score              | 23.0 (19.5–26.5) | 25.0 (20.0–27.0) | 0.225   |
| Visuospatial/executive function | 3.0 (2.0–4.5) | 4.0 (3.0–5.0) | 0.465   |
| Naming                   | 3 (2–3)     | 3 (3–3)                  | 0.271   |
| Attention                | 6.0 (4.0–6.0) | 6.0 (4.5–6.0) | 0.861   |
| Abstraction              | 1 (1–2)     | 1 (1–2)                  | 0.648   |
| Language                 | 2 (2–3)     | 3 (2–3)                  | 0.122   |
| Delayed memory           | 2.0 (1.0–4.0) | 3.0 (0.5–4.0) | 0.673   |
| Orientation              | 6 (5–6)     | 6 (5–6)                  | 0.080   |
| STT-A, s                 | 83.0 (60.5–120.0) | 68.0 (49.0–86.5) | 0.010   |
| STT-B, s                 | 204.0 (151.5–294.5) | 153.0 (126.5–212.5) | 0.015   |
| STT-B-1 min              | 8.0 (5.0–11.0) | 9.0 (7.0–13.0) | 0.056   |
| STT B-A, s               | 115.0 (78.0–146.5) | 94.0 (69.5–126.0) | 0.117   |
| STT B/A                  | 2.2 (1.9–2.6) | 2.4 (2.1–2.8) | 0.265   |
| Stroop-A (time), s       | 33.0 (30.0–44.5) | 32.0 (26.0–37.0) | 0.116   |
| Stroop-A (correct)       | 50.0 (50.0–50.0) | 50.0 (50.0–50.0) | 0.139   |
| Stroop-B (time), s       | 63.0 (51.0–73.0) | 55.0 (41.0–74.5) | 0.169   |
| Stroop-B (correct)       | 49.0 (46.0–50.0) | 49.0 (47.0–50.0) | 0.343   |
| Stroop-C (time), s       | 103.0 (87.5–134.0) | 97.0 (71.0–121.0) | 0.124   |
| Stroop-C (correct)       | 46.0 (41.0–49.0) | 49.0 (45.0–50.0) | 0.035   |
| SIE time consuming, s    | 46.0 (31.5–60.0) | 36.0 (22.0–56.0) | 0.204   |
| SIE right numbers        | –2.0 (–4.0–0.0) | 0.0 (–2.5–0.0) | 0.094   |

*Statistically significant. Data are presented as n (%) or median (interquartile range). BAD: Branch atheromatous disease; CSVD: Cerebral small vessel disease; MoCA-BJ: Beijing version of the Montreal Cognitive Assessment; STT: Shape Trail Test; STT-A: Shape Trail Test A; SCWT: Stroop Color and Word Test; SSI: Single subcortical infarction; SIE: Stroop interference effects.

### Table 3: A generalized linear model for analyzing the association between different etiological mechanisms and cognitive function in patients with SSI.

| Variables                   | STT-A β coefficient (95% CI) | P value | STT-B β coefficient (95% CI) | P value | Stroop-C (correct) β coefficient (95% CI) | P value |
|-----------------------------|-------------------------------|---------|-------------------------------|---------|-----------------------------------------------|---------|
| Age                         | 1.743 (1.078–2.408)           | <0.001  | 3.221 (2.188–4.254)           | <0.001  | –0.108 (–0.228–0.011)                          | 0.076   |
| Education                   | –4.542 (–6.200 to –2.884)     | <0.001  | –7.671 (–10.246 to –5.106)    | <0.001  | 0.492 (0.195–0.790)                           | 0.001   |
| NIHSS                       | –0.605 (–2.896–1.687)         | 0.630   | 2.167 (–1.392–5.726)          | 0.223   | 0.107 (–0.304–0.518)                          | 0.611   |
| Lesion location             | 0.970                         | –       | 0.968                         | –       | 0.917                                         |         |
| Thalamus                    | 1.063 (–20.732–22.857)        | 0.924   | 6.813 (–27.036–40.662)        | 0.693   | 1.093 (–2.818–5.005)                          | 0.584   |
| Internal capsule            | 2.108 (–15.472–19.689)        | 0.814   | 3.322 (–23.982–30.626)        | 0.812   | –0.268 (–3.423–2.888)                         | 0.868   |
| Putamen and pallidum        | 4.162 (–12.982–21.305)        | 0.634   | –0.510 (–27.136–26.115)       | 0.970   | 0.112 (–2.963–3.188)                          | 0.943   |
| Other location              | Ref                           | –       | Ref                           | –       | Ref                                           | –       |
| CSVD-related SSI            | –16.168 (–29.363 to –2.972)   | 0.016   | –23.347 (–43.841 to –2.853)   | 0.026   | 1.766 (–0.602–4.134)                          | 0.144   |
| BAD                         | Ref                           | –       | Ref                           | –       | Ref                                           | –       |

*Statistically significant. BAD: Branch atheromatous disease; CSVD: Cerebral small vessel disease; CI: Confidence interval; NIHSS: National Institutes of Health Stroke Scale; Ref: Reference; STT: Shape Trail Test; STT-A: Shape Trail Test A; SSI: Single subcortical infarction.
Most clinicians have difficulty in distinguishing between BAD and CSVD-related SSI. We previously found that the number of axial lesion slices (≥3), although with marginal significance, provided a better appreciation of the discrepancy of infarct compared to axial lesion diameter for predicting the mechanism of recent subcortical infarction. High-resolution MRI showed that patients with plaques presented larger infarction lesions and more proximal lesions compared to those patients without plaque, which was consistent with the imaging features of BAD. The present study defined BAD as having a larger infarct diameter and more infarct layers compared to CSVD-related SSI, resulting in more serious cognitive impairment. While the NIHSS score is an established predictor of functional outcomes after stroke, it lacks a cognitive component, and its relationship with cognitive outcomes is controversial. Yamamoto reported a higher initial NIHSS score in patients with BAD than in patients with lipohyalinotic degeneration. Fure et al found that a neurologic deficit according to NIHSS was related to common cognitive variables in a bivariate analysis but not in the multivariate model, partly due to the relatively low NIHSS scores in patients with lacunar stroke. In our study, the NIHSS score at admission was also higher in the BAD group than that in the CSVD-related SSI group, which may partly explain the worse cognitive status of BAD patients. However, we observed no significant differences in CSVD MRI markers between the two groups. In other words, the burden of CSVD in patients with BAD remained substantial.
We performed correlation analyses to study the relationships between the MoCA-BJ, STT, and SCWT. The MoCA-BJ was significantly correlated with the STT and SCWT, except for STT B/A. The high correlations between STT and global cognition were consistent with those reported by a Chinese study.\(^\text{[13]}\) Our data showed that STT-B was most related to global cognition in patients with SSI [Table 4]. The results of our analysis also revealed that STT-A and STT-B correlated well \((r = 0.863)\). However, the Stroop-C (correct) correlated only moderately with the STT-A \((r = 0.524)\) and STT-B \((r = 0.586)\), suggesting that they measure somewhat different functions.

In our study, a higher correlation was found between STT (especially STT-B) and MoCA-BJ in SSI patients. Therefore, we established reference data for STT-A and STT-B in patients with SSI. The AUCs of the ROC curves in the BAD group were 0.821 and 0.824 for STT-A and STT-B, respectively, while the AUCs of the ROC curves in the CSVD-related SSI group were 0.701 and 0.729 for STT-A and STT-B, respectively. In addition, the sensitivity and specificity were acceptable.

Both BAD and CSVD-related SSI patients had low NIHSS scores \((5 \pm 2-7, n = 2 \pm 1-4, P = 0.001)\). Although the difference in NIHSS scores between the groups was statistically significant, the clinical manifestations of SSI patients were mainly pure motor or pure sensory deficits, and cognitive function was not generally affected by the disease itself. Patients with mild stroke present a new challenge for rehabilitation specialists because their primary deficits are more subtle than the typical stroke symptoms that are more overt.\(^\text{[33]}\) Despite rehabilitation training, the greatest concern is the degree of physical dysfunction and not cognitive dysfunction. However, cognitive impairment after a mild stroke can severely impact an individual’s ability to function in everyday life and perform meaningful occupations.\(^\text{[33-35]}\) Early identification of post-stroke cognitive impairment may contribute to a favorable outcome; thus, clinical interventions in the acute phase may be beneficial for the quality of life of patients with mild ischemic stroke.

This study has several limitations. First, the sample size was small, limiting our statistical power; thus, large-scale studies are needed to verify our results. Second, we excluded patients with hearing disorders, communication disorders, color blindness, color weakness, and severe paralysis, which might have affected the accuracy of the executive tests. Third, we did not evaluate cerebral microbleed because some patients failed to complete the relevant MRI studies; however, none of the patients had a history of cognitive dysfunction. Fourth, we lacked a control group for comparing the MoCA-BJ, STT, and SCWT between healthy people and patients with SSI. Fifth, we cannot fully explain why the cognitive impairment in BAD patients was more severe than that in CSVD-related SSI patients. Interpreting the cognitive impairment mechanisms underlying the two types of SSI requires further research. Finally, follow-up of cognitive and functional outcomes is warranted to investigate the role of STT and SCWT in the prediction of long-term cognitive and functional outcomes after SSI.

In conclusion, the results of our study indicated that BAD patients were more likely to perform worse than CSVD-related SSI patients in the domains of language, attention, executive function, and memory. In addition, the STT-B was most related to global cognition in patients with SSI, suggesting the sensitivity of this test in detecting executive dysfunction and global cognition impairment. Future research is needed to fully elucidate the cognitive impairment features after BAD, which may contribute to the prevention rather than the treatment of PSCI.

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**Conflicts of interest**

None.

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