# Processing Speed is Associated with Infarct Volume and Global Subcortical Ischemic Vasculopathy (SIV) while Set Shifting is Associated with Targeted Cholinergic SIV Alone

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## Background

- **Post-stroke cognitive impairment (PSCI)** – typified by deficits in information processing speed and executive function [1,2] – is related to the size and location of infarctions, as well as the degree of co-morbid atrophy and ischemic vasculopathy. [3,4]
- Ischemic vasculopathy, seen as **White Matter Hyperintensities (WMH)** on Magnetic Resonance Imaging (MRI), has been independently associated with decline in information processing speed and executive function.[5]
- WMH in lateral cholinergic pathways have been associated with executive dysfunction as well, suggesting that the cholinergic system may be a substrate of executive function. [6,7]
- Improved performance on executive tasks, such as the Trail Making Test (TMT), has been reported in patients with subcortical lacunar strokes treated with cholinesterase inhibitors[8]

## Purpose

- The potentially distinct influences of ischemic infarction, global WMH and cholinergic WMH on speed of processing and executive function are not well established.
- We use volumetric MRI coupled with the Trail Making Test, which assesses both processing speed (TMT-A) and set-shifting (TMT-B and TMT-B-A-difference-of-score), to better define these relationships in patients with acute ischemic territorial stroke.

## Methods

### 1. Study Participants

- 46 participants with acute ischemic stroke were recruited
- Inclusion criteria: no other neurodegenerative diseases, and able to complete neuropsychological testing

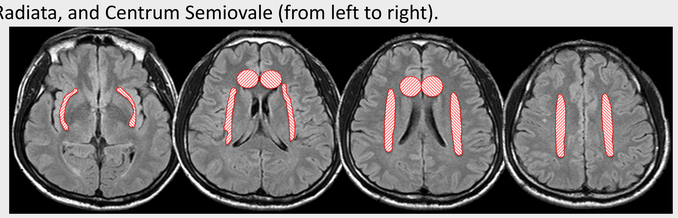
### 2. Magnetic Resonance Imaging

- T1-weighted, T2-weighted, Diffusion Weighted Imaging (DWI), and FLAIR images were acquired on 1.5T Philips MRI scanner at Hallym University Hospital in South Korea within four days of stroke event

### 3. Image Processing

- Acutely infarcted tissues (hyperintense on DWI) and previous covert infarctions (hypodensity on T1) were traced using ANALYZE 8.0 software.
- WMH on FLAIR images were assessed using (i) **The Cholinergic Pathways HyperIntensity scale (CHIPS)** [7] and (ii) a semi-automated fuzzy lesion extractor (FLEX) pipeline [9]
- T1- based brain tissue segmentation was achieved using a modified in-house Semi-Automatic Brain Region Extraction (SABRE) Pipeline [10]

**Figure 1:** Lateral cholinergic and cingulate cholinergic pathway regions visually assessed using the CHIPS rating. Low External Capsule, High External Capsule, Corona Radiata, and Centrum Semiovale (from left to right).



### 4. Neuropsychological Assessment

- 3 months after stroke, MMSE (Mini-Mental State Exam) as well as TMT-A and TMT-B were administered
- The derived score from the difference between TMT-B and TMT-A (TMT-B-minus-TMT-A time) was used as a purer metric of set-shifting executive function.

### 5. Statistical Analysis

- Using Microsoft SPSS 20.0 Software, multiple linear regression analyses with backwards elimination of non-significant variables were performed
- Normal Appearing Brain Parenchymal Fraction (BPF), infarction volume, CHIPS rating score, and global WMH volume, as predictors of (i) TMT-A and (ii) TMT-B-minus-TMT-A
- Age, sex, education and strategic stroke location were controlled for in all analyses

## Results

**Figure 2:** 68 year old patient with right thalamic stroke (0.50mL or 0.04% of TIV), some global WMH (1.97mL or 0.2% of TIV) and very few WMH in cholinergic projections (CHIPS = 8/100 ). TMT-A time=32 seconds ; TMT-B time=45 seconds ; TMT-B-minus-TMT-A=13 seconds)

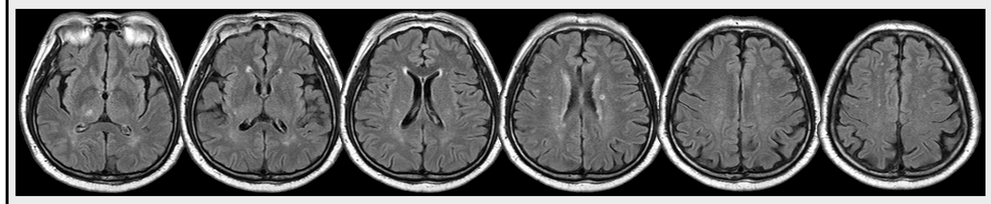


**Figure 3:** 80 year old patient with multiple acute strokes in right MCA territory and old infarct in right inferior insula (5.35mL or 0.58% of TIV), moderate-severe global WMH (19.31mL or 1.6% of TIV) and WMH in cholinergic projections (CHIPS = 34/100 ). TMT-A time = 123 seconds ; TMT-B time=300seconds ; TMT-B-minus-TMT-A time= 177 seconds)

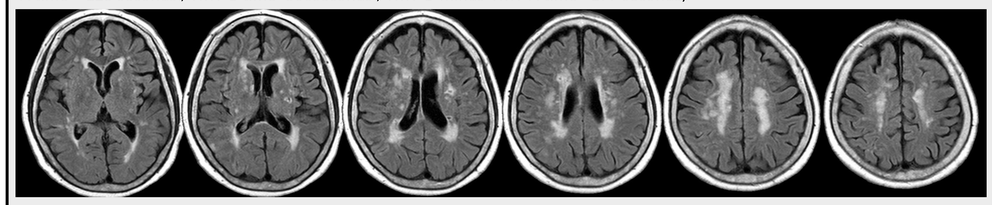


**Table 1:** Patient Demographics (N=46)

| Variable | Mean ± SD |
|---|---|
| **Demographics and clinical features** | |
| Men/Women | 23/27 |
| Age | 64.2 ± 13.9 |
| Years of Education | 8.9 ± 5.1 |
| MMSE | 24.2 ± 5.1 |
| NIHSS at stroke onset | 2.9 ± 2.7 |
| NIHSS at 3 months | 1.1 ± 2.0 |
| **Vascular Risk Factors** | |
| Hypertension | 64% |
| Hyperlipidemia | 24% |
| Diabetes Mellitus | 28% |
| Coronary Artery Disease | 12% |
| Atrial Fibrillation | 24% |
| **Neuropsychological Testing** | |
| Trails Making Test-A | 57.87 ± 58.58 |
| Trails Making Test-B | 132.023 ± 111.55 |
| TMT-B - TMT-A Difference Score | 81.46 ± 82.90 |

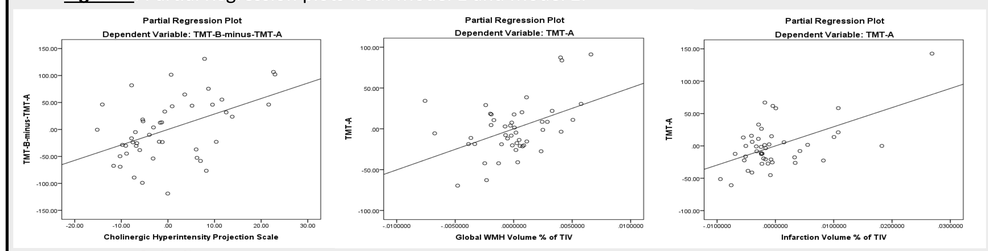
**Table 2:** Volumetric Data (N=46)

| Variable | Mean ± SD |
|---|---|
| **Neuroimaging measures** | |
| Mean count of acute strokes | 1.96 ± 4.43 |
| Number with previous strokes | 25 |
| Mean count of previous strokes | 1.72 ± 0.98 |
| CHIPS | 13.62 ± 11.42 |
| **Volumetric Measures (mL)** | |
| Acute infarction | 5.24 ± 8.88 |
| Chronic infarction | 7.44 ± 20.95 |
| Total infarction volume | 9.04 ± 16.92 |
| Total Intracranial Volume | 1290.55 ± 121.49 |
| **Volumetric Percentages (%)** | |
| Total Infarction | 0.73 ± 1.47 |
| WMH | 0.37 ± 0.43 |
| GM | 45.80 ± 5.92 |
| WM | 33.72 ± 5.07 |
| vCSF | 2.38 ± 1.29 |
| sCSF | 16.99 ± 2.89 |
| NABPF | 79.54 ± 4.34 |

**Table 3:** Summary of Linear and Regression Analyses. Note: Model 3 is re-run with the exclusion of those patient's whose strokes involved cholinergic pathways.

| | Variable | Standardized β | p-value | $r^2$ |
|---|---|---|---|---|
| **Processing Speed (TMT-A)** | | | | |
| Model 1 (N=46) | Years of Education | -0.371 | 0.0001 | 0.11 |
| | Global WMH Volume | 0.374 | 0.002 | 0.06 |
| | Total Infarct Volume | 0.700 | 0.0001 | 0.44 |
| **Set-Shifting (TMT-B-minus TMT-A)** | | | | |
| Model 2 (N=46) | Age | 0.515 | 0.0001 | 0.20 |
| | CHIPS | 0.386 | 0.001 | 0.11 |
| Model 3 (N=32) | Age | 0.580 | 0.0001 | 0.24 |
| | CHIPS | 0.341 | 0.01 | 0.08 |

**Figure 4**: Partial Regression plots from Model 1 and Model 2.




**Summary of Findings:**

- Fewer years of education, increasing infarct volume, and increasing global WMH volume were associated with worse speed of processing
- Only increasing age and increasing CHIPS rating was associated with worse set shifting
- When those with stroke involvement in the lateral cholinergic projections were excluded (N=14), the association between CHIPS and set shifting executive function remained
- Both increasing Global WMH volume (rho=0.484, p=0.0001) and increasing CHIPS severity (rho=0.324, p=0.02), were correlated with hypertension

## Discussion and Conclusion

- Here we report the differential influences of global WMH, cholinergic WMH and ischemic infarction on processing speed and set-shifting executive function
- These findings were noted after Bonferroni correction for multiple comparisons and after controlling for the effects of age, gender, education, global atrophy (NABPF), and strategic stroke location
- This suggests that the degree of WMH in cholinergic pathways alone is sufficient to impair set-shifting executive dysfunction in PSCI
  - In the context of PSCI, the relationship between stroke and executive dysfunction may be more related to the effects of stroke on processing speed than directly on executive dysfunction.
  - Also plausible, is that the presence of territorial stroke may lower the threshold of WMH in cholinergic projections that would be necessary to produce an executive dysfunction.
- In addition, hypertension was associated with global WMH volume and the extent of WMH in cholinergic projections.
  - This reemphasizes the importance of appropriately managing hypertension in stroke patients
- Cognitive neurorehabilitation targeting set-shifting may be helpful in PSCI, and since damage to the cholinergic system appears to be a substrate for set-shifting executive dysfunction, this could also be a target of cholinergic pharmacotherapy.
- The significance of the TMT is more than its assessment of processing speed and executive function; it also has broad implications in the health and safety of patients with cognitive impairment and dementia, as it is also predictive of driving ability. [11]

## Acknowledgements

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