Location of White Matter Hyperintensities Is Important For Set-Shifting but not Processing Speed in Mild Cognitive Impairment and Alzheimer's Disease

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Background

- Subcortical Ischemic Vascular Disease (SIVD), manifests as white matter hyperintensities (WMH) on Proton Density/T2-weighted MRI [1]
- Although associations between WMH and global cognitive performance, processing speed, and executive function have been reported, these results have been inconsistent and may be related to:
  i. Threshold effect of WMH[2]
  ii. Different operational definitions of cognitive measures [3]
  iii. Different regional effects of WMH[2]
- The Trail-making Test (TMT) is a validated measure of **speed of processing** (part A; TMT-A) and **set-shifting executive function** (part B; TMT-B). [4,5]
- WMH burden is worse in Alzheimer's Disease compared with normal aging , however, the relationship between executive dysfunction and WMH remains uncertain.

Purpose and Hypothesis

To investigate the association between TMT performance (speed of processing by TMT-A; set-shifting executive function by TMT-B) and regional periventricular and deep WMH in individuals with MCI and AD.

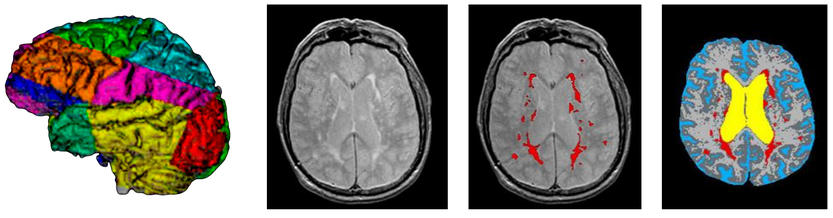
Methods and Analysis

Table 1: Demographic and Volumetric Data

	N=158
Demographics & Neuropsych	
Age, years	71.31 ± 9.88
Male:Female	77:81
Education, years	13.83 ± 3.70
MMSE	24.91 ± 3.39
TMT-A (seconds)	60.68 ± 35.33
TMT-B (seconds)	178.66 ± 91.30
Volumetric Data	
TIC (mL)	1207.37 ± 137.90
Parenchyma (mL)	896.98 ± 105.97
NAGM (mL)	522.35 ± 55.73
NAWM (mL)	374.64 ± 59.90
Ventricles (mL)	46.13 ± 22.29
Global WMH (mL)	5.42 ± 7.47
Deep WMH (mL)	0.86 ± 1.17
Periventrciular WMH (mL)	4.56 ± 6.93

- MRIs were acquired from patients participating in the Sunnybrook Dementia Study [6] : AD (N=131) and MCI (N=27). TMT-A and – B were administered within 3 months of MRI acquisition.
- Two analyses were conducted and included subjects if they:
  1. Had No ceiling effect present at 240 seconds on TMT-B (N=158)
  2. Had >10cc of global WMH, and no ceiling effect present at 240 seconds on TMT-B (N=21)
- Brain tissue volumetric segmentation on MRI was achieved using the Semi-Automatic Brain Region Extraction (SABRE) Pipeline. [7] Regional parcellation and volumetrics of WMH was quantified using the Lesion Explorer pipeline[8].
  - ROIs included: frontal lobe, parietal lobe and basal ganglia and thalamus
- Regional normal appearing gray matter (NAGM), periventricular WMH and deep WMH volumes were assessed as predictors in multiple linear regression models. All models were co-varied for age, sex, and education. All volumetric variables were head size corrected.

Figure 1: SABRE regional parecellation (left) Lesion Explorer (right)



Findings

Table 2: Summary of Linear Regression Analyses

	Analysis 1				Analysis 2			
	Whole Sample (N=132)				WMH >10cc of TIC (N=21)			
	Significant Variables	Standardized β	p-value	r^2	Significant Variables	Standardized β	p-value	r^2
Processing Speed (TMT-A)								
Global Volumetric Analysis	Age	-0.223	0.019	0.04	Global WMH	0.527	0.04	0.21
	NAGM	-0.38	0.0001	0.12				
Regional Volumetric Analysis	Age	-0.174	0.04	0.03	None	N/A	N/A	N/A
	NAGM	-0.342	0.0001	0.11				
Executive Function (TMT-B)								
Global Volumetric Analysis	NAGM	-0.422	0.0001	0.17	None	N/A	N/A	N/A
Regional Volumetric Analysis	Frontal lobe pWMH	0.232	0.01	0.04	Frontal lobe pWMH	0.467	0.03	0.20
	NAGM	-0.428	0.0001	0.17				

Figure 2: Demonstration of substantial WMH burden in a 69 year old patient with AD.
TMT-A= 88 seconds WMH volume = 37.33cc
TMT-B= 423 seconds %WMH = 3.1% of Supratentorial-TIC

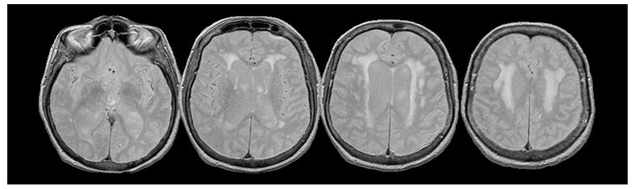


Figure 3: Demonstration of less WMH burden in a 71 year old patient with AD.
TMT-A= 34 seconds WMH volume = 7.34cc
TMT-B= 68 seconds %WMH = 0.5% of Supratentorial-TIC

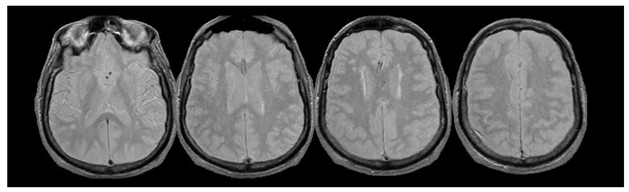
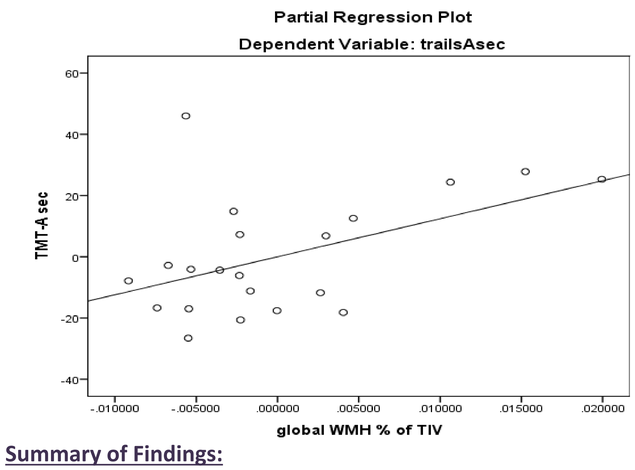


Figure 3: Partial Regression Plot for **Analysis 2** WMH > 10cc of STIC (A) Global Volumetric Analysis and (B) Regional Volumetric Analysis



Summary of Findings:

- Analyses revealed that global WMH were associated with processing speed only with the inclusion of those whose WMH exceeded the 10cc WMH threshold proposed by Boone et al 1992.
- Set shifting was related to frontal lobe pWMH
  - However, frontal lobe pWMH explained a much larger proportion of variance in TMT-B performance in those with more than 10cc of WMH

Discussion and Conclusions

- These results suggest that there is regional specificity to the effect of WMH on set-shifting executive function but that localization is less important for speed of processing.
- Our analyses also demonstrate different effects depending on whether the WMH threshold effect is accounted for, which may partly explain why WMH location has been inconsistently linked to cognitive dysfunction
- Global WMH was associated with processing speed in those with >10mL of WMH lesion volume
- In both analyses, frontal periventricular WMH were important for set-shifting executive dysfunction, but in those with >10cc of global WMH, pWMH accounted for 20% of total variance in TMT-B
- This suggests the need for careful operational definitions of different executive function tasks in brain behavior research, especially in the presence of WMH

Acknowledgements

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