Normal Appearing Tissue is Related to Vascular Cognitive Impairment in Chronic Stroke Patients

Kie Honjo[1,2], David L. Nyenhuis[3], Fu-qiang Gao[1,2], Christopher J. M. Scott[1,2], Anoop Ganda[1,2], Nancy J. Lobaugh[2], Simon J. Graham[2], X. J. Zhou[4], Novena Rangwala[4], Glenn T. Stebbins[5], Jennifer Marola[4], Erin Gibson[6], Alicia A. McNeely[1,2], Donald T. Stuss[2,6], Sandra E. Black[1,2,6,7]

1. Heart and Stroke Foundation Centre for Stroke Recovery (Sunnybrook Site), University of Toronto (U of T), Toronto, ON, Canada; 2. Brain Sciences Program, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, U of T, Toronto, ON, Canada; 3. Hauenstein Neuroscience Center, Saint Mary's Health Care, Grand Rapids, MI, USA; 4. University of Illinois-Chicago Medical School, Chicago, IL, USA; 5. Rush University Medical Center, Chicago, IL, USA; 6. Rotman Research Institute, Baycrest, University of Toronto, Toronto, ON, Canada; 7. Toronto Dementia Research Alliance, Toronto, ON, Canada

I. BACKGROUND

- Post-stroke cognitive impairment is a very common finding in patients with focal brain infarction, affecting up to 2/3 of stroke survivors[1].
- Neuropsychological testing in this population generally shows greater executive function impairment than memory impairment, especially in mild cases.
- Executive function in ischemic stroke patients also inversely correlates with white matter hyperintensities (WMH)[2].
- Brain atrophy after large infarcts are known to have an unfavorable functional outcome[3].
- Using neuropsychological and MRI protocols recommended by the Vascular Cognitive Impairment (VCI) harmonization criteria[4], we set out to see whether normal appearing (NA) tissue volumes correlated with neuropsychological testing scores.

II. OBJECTIVES

To examine the relationship between normal appearing tissue volumes and cognitive functions in patients with chronic focal brain infarction.

III. METHODS

Participants:

- 59 subjects, 6-36 months post-infarct
- All subjects were administered
  (1) The 60 minute protocol (VCI-60min),
  (2) The 30 minute protocols (VCI-30min)[4]
  (3) Montreal Cognitive Assessment (MoCA)[5].
- MRI: within 3 weeks of neuropsychological testing.

MR Technique:

GE, 3-Tesla (3D-T1, T2/PD, FLAIR)

1. **Brain tissue segmentation** (FIGURE1)
   Semi-automated brain extraction (SABRE)[6],
   Segments into Gray matter (GM), White matter (WM), ventricular & sulcal CSF, and WMH
2. **Infarction tracing** (FIGURE2)
   Focal infarcts were visually identified and manually traced on axial T1 including the peri-infarct hyper-intensity. (FLAIR & PD/T2 coregistered to T1)

Used ANALYZE 8.0 or ITK-snap.

3. **Brain parenchymal fraction (BPF)**
   BPF = Normal appearing WM (NAWM)
   + Normal appearing GM (NAGM)

- All derived volumes were divided by supra-tentorial total intracranial capacity (STIC) to correct for individual head size (normalized brain volume)[6].

Neuropsychological testing:

- The VCI-60min & VCI-30min tested executive, language, visuospatial, and memory functions.
- Z scores were computed for both protocols, each domain, and MoCA.

Statistical Analysis:

Multiple regression modeling forced entry of age and education first, and then assessed brain volumetric measures to predict scores on MoCA, VCI-60min, VCI-30 min, and each domain.

IV. RESULTS

TABLE1. Demographic and Brain-MRI variables

Variables (N=59)	Mean ± SD (median, range)
Age (years)	65.0 ±13.0 (62, 45-89)
Stroke side (L/R)	32 / 27
MMSE	27.2 ±3.0 (28, 20-30)
MRI	
STIC (cm^3)	1208 ±136
BPF (cm^3)	899.6 ± 118.0
Infarct volume (cm^3)	29.3 ± 51.9
WMH (cm^3)	11.5 ± 20.1

STIC-total intracranial capacity; BPF-Brain parenchymal fraction

FIGURE1: Brain tissue segmentation (SABRE)

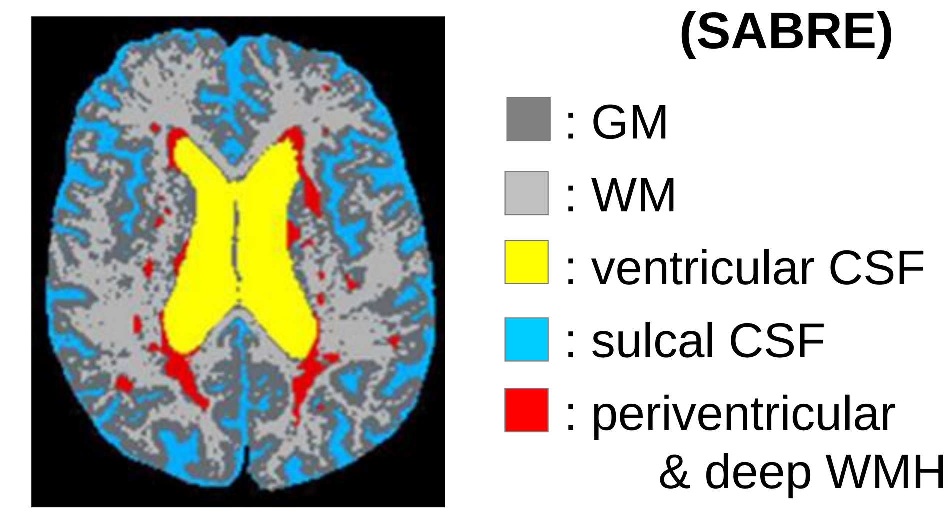
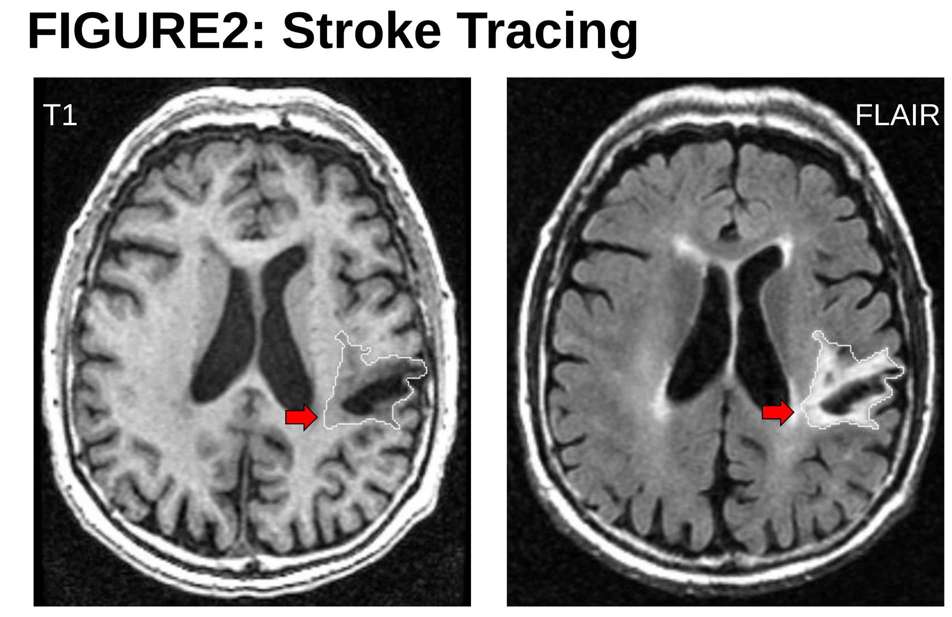


FIGURE2: Stroke Tracing



Left: Axial T1 image
Right: FLAIR image co-registered in T1 space

TABLE2. Multiple regression analysis :

- All testing and domain scores were predicted by age except for visuospatial performance
- Years of education did not predict any testing scores
- Blue boxes indicates significant association with the brain volumetric measurement themselves.
- Purple boxes indicates the measurements improve the model over age effects alone

Predictors	MoCA	VCI-60min	VCI-30min	Executive	Language	Visuospatial	Memory
BPF (NAGM+WM)	b=0.4 † R^2=0.16 F=10.75	b=0.58 ‡ R^2=0.34 F=27.2	b=0.5 ‡ R^2=0.25 F=18.71	b=0.6 ‡ R^2=0.35 F=29.64		b=0.41 † R^2=0.17 F=11.34	
NAGM				b=0.284* R^2=0.23 ΔR^2=0.73 F=7.71*			
NAWM	b=0.53 ‡ R^2=0.28, F=21.76	b=0.64 ‡ R2=0.45, F=36.75	b=0.53 ‡ R2=0.28 F=21.81	b=0.63 ‡ R2=0.39 F=34.91		b=0.51 ‡ R2=0.26 F=19.90	b=0.4 † R2=0.16 F=10.78
NAGM_Left		b=0.29* R^2=0.24 ΔR^2=0.65 F=8.29*		b=0.33* R^2=0.24 ΔR^2=0.087 F=8.03*			
NAGM_Right							
NAWM_Left	b=0.62 ‡ R^2=0.38, F=33.96	b=0.59 ‡ R2=0.35 F=29.19	b=0.45 ‡ R2=0.21 F=14.50	b=0.58 ‡ R2=0.33, F=26.61	b=0.43 † R2=0.18 F=12.4	b=0.45 ‡ R2=0.20 F=14.34	
NAWM_Right		b=036 † R^2=0.29, ΔR^2=0.115 F=10.75*	b=033* R^2=0.23 ΔR^2=0.98 F=8.01*	b=037 † R^2=0.27, ΔR^2=0.122 F=10.02 ‡		b=039 † R^2=0.15, F=10.18*	

MoCA, Montreal Cognitive Assessment; NAGM_Left, total of NAGM in the left hemisphere; NAGM_Right, total of NAGM in the right hemisphere; NAWM_Left, total of NAWM in the left hemisphere; NAWM_Right, total of NAWM in the right hemisphere; * $p<0.05$; † $p<0.01$; ‡ $p<0.001$

V. DISCUSSION & CONCLUSIONS

- This study demonstrates that BPF including NAWM was strongly associated with MoCA total score as well as VCI Harmonization 60 & 30 Minute batteries, in which executive and visuospatial functions showed similar associations after accounting for age.
- NAGM itself did not show any significant association.
- Language function was predicted only by left NAWM and memory was predicted only by total NAWM. Right NAWM only showed contribution to visuospatial function.
- Expected laterality was seen in language (left) and visuospatial (right) function only in WM. .
- Residual NA tissue on MRI may be more important in predicting post-stroke cognition, more so than NAGM alone or tissue lost due to infarct damage.
- . WM connectivity appears more important than remaining GM in cognitive correlations
- Healthy white matter connections may be important for understanding brain behaviors relations post-stroke.

Acknowledgement: We gratefully acknowledge our participants, and financial support from NIH/NINDS NS 057514, L.C. Campbell Foundation, and Heart and Stroke Foundation Centre for Stroke Recovery

References: 1) Madureira S, et al. *Eur J Neurology 2001.;* 2) Muir R, et al. Poster #180 Neuroimaging biomarkers reflect post stroke cognitive impairment measured by the vascular cognitive impairment harmonization standards neuropsychology protocol.; 3) Lee SH, et al. *JNNP* 2010.; 4) Hachinski V, et al, *Stroke 2006.;* 5) Nasreddine ZS et al. *J Am Geriatr Soc 2005*.; 6) Ramirez J et al. *Neuroimage 2011*.