Relationships between Large Artery Cerebrovascular Disease, Substantia Innominata, and Cognition in Normal Aging, Subcortical Vasculopathy & Alzheimer's Disease

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Introduction

Cholinergic Deficit in AD:

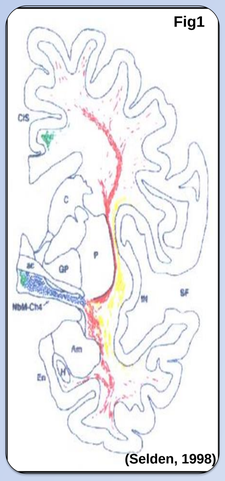
Degenerative Processes

- Alzhiemer's disease (AD) is characterized by degeneration of cholinergic neurons in the nucleus basalis of Meynert (nBM), which forms part of the substantia innominata (SI).[1]
- SI volume loss results in ↓ ascending cholinergic input to all cortical regions and the amygdala via medial and lateral pathways (Fig 1),[2] and correlates with severity of dementia and MMSE score.[3]

Vascular Processes

- Ischemic white matter hyperintensities (WMH),[4] an index of subcortical ischemic vasculopathy (SIV), may represent microvascular ischemia.
- Greater prevalence of microvascular ischemic disease is associated with reduced cognitive performance in AD, in part related to strategic compromise of cortical cholinergic projections from the nBM.[5]
- AD patients also have greater burden of macrovascular disease[6] but the mechanism whereby macrovascular disease exacerbates cholinergic pathway dysfunction is less clear.

Fig1



Internal Carotid Artery Impingement of SI in AD

- **Gao et al. (2013)**[7] recently proposed that internal carotid artery termination (CAT) elongation, related to long-standing vascular risk factors[8], correlates with reduced SI volume, possibly through mechanical impingement or occlusion of arterial branches supplying the SI (Fig 2).

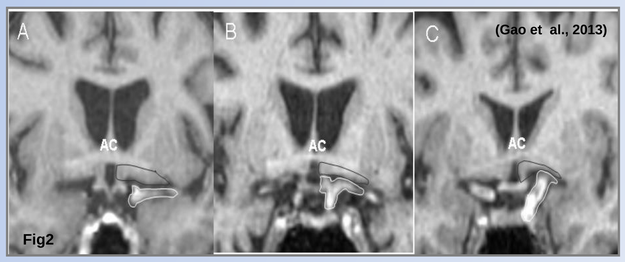


Fig2

Objective

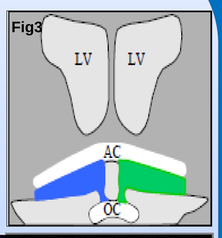
To replicate Gao et al.'s findings in AD patients and investigate whether correlations exist in patients with cerebrovascular disease (TIA/stroke) with or without primary degenerative processes of dementia

Methods

Participants

105 subjects were recruited from the Sunnybrook Dementia Study
- **NC:** 30 age- and education- matched controls
- **SIV:** 26 non-demented patients with TIA/stroke and moderate/severe WMH
- **AD:** 29 AD patients with minimal WMH
- **AD + SIV:** 20 AD patients with moderate to severe WMH

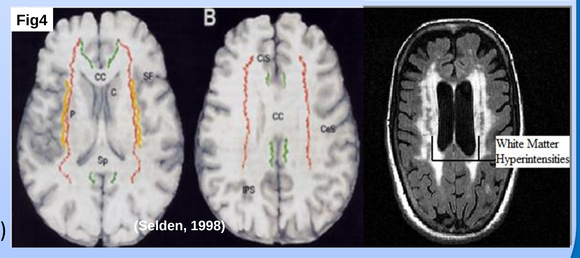
Fig3



•MR Imaging Data

1)SI Volume adjusted for total intracranial capacity (TIC) (Fig 3)
2)CHIPS Score /100 (Fig 4)
3)Brain/Hippocampal/Lesion Volume adjusted for TIC

Fig4



•Carotid (CAT) Pathology Measures

1)Severity of CAT impingement on SI rating (0-12) (Fig 2)
2)Carotid elongation above clivus (mm)

•Neuropsychological Test Battery

Results

•SI volume was similar in AD and SIV groups (Cohen's d:ADvs.NC 0.85; SIVvs.NC 0.88) but worse in AD+SIV (Cohen's d=1.11) compared to NC (*F*=5.98, p=0.001) (Fig 5).

•Smaller **SI volume** correlated with higher CHIPS scores (Spearman's rho=-0.25, p=0.035), carotid rating scores (Spearman's rho=-0.35, p=0.002), and greater internal carotid elongation (Spearman's rho= -0.32, p=0.005) in all patients (Table 1).

•CHIPS was significantly higher in AD+SIV and SIV compared to NC and AD (*F*=21.78, p<0.0005). **SI & CHIPS** explained 19.9% of the variance in memory scores.

Fig5

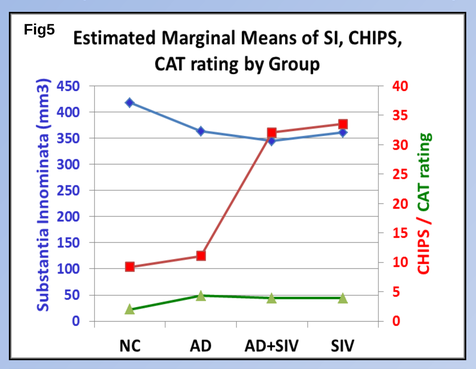
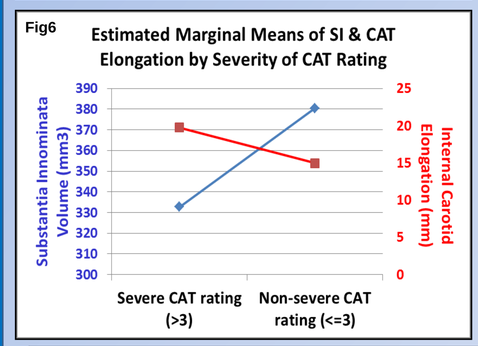


Fig6



•CAT impingement rating score was significantly higher in all patient groups compared to NC (*F*=2.93, p=0.029). Those with **severe cat rating** had significantly smaller SI volumes (*F(1,70)*=12.92; p=0.001; Cohen's d=0.85), and significantly longer internal carotid lengths (*F(1,69)*=14.31; p<0.0005; Cohen's d=0.90) (Fig 6).

•CAT elongation correlates with poorer scores on executive function in all patient groups (Spearman's rho=-0.26, p=0.031), with a trend toward worse MMSE scores (Spearman's rho=-0.21, p=0.079). Addition of **CAT elongation** in stepwise regression improved prediction of SI to the greatest extent compared to other variables (R2change= 0.148, F(6,66)=14.78; p<0.0005) (Fig 7).

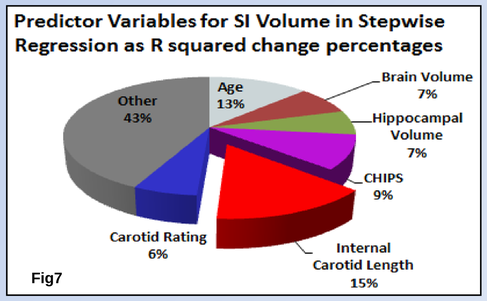


Fig7

Bivariate Correlations between Imaging, Vascular and Cognitive Z Scores in all Patient Groups

Table 1	SI Volume	CHIPS	Carotid Rating	MMSE	Attention/Working Memory	Executive Function
Total SI/TIC		*-.247 (p=.035)*	*-.443 (p=.000)*		*.426 (p=.030)**	
Internal Carotid Length	*-.323 (p=.005)*		*.352 (p=.002)*	*-.207 (p=.079)*		*-.256 (p=.031)*

* SIV population only

Discussion

•**SI volumes** were similar in AD & SIV groups, and correlated negatively with CHIPS, CAT elongation, and CAT rating, while helping to predict memory scores.

•Patients with severe **CAT ratings** had significantly smaller SI volumes and longer CAT lengths, suggesting that impingement of the internal carotid may relate to reduced SI volume (Fig 8a&b).

•**CAT length** correlated with poorer executive function scores, with a trend toward worse MMSE scores. CAT elongation significantly improved prediction of SI volume to the greatest extent compared to all other variables in regression.

•All patients had higher carotid ratings than NC, suggesting **macrovascular disease** and possibly increased vascular risk factors in both AD and SIV groups.

•Similar SI volume in AD & SIV groups suggests that **cholinergic depletion** in the SI can occur through primary SI degeneration as in AD, or through retrograde degeneration of cholinergic tracts from strategically placed WMH in SIV.

•The combination of **degenerative & microvascular disease** in AD+SIV resulted in smallest SI volumes, largest CAT lengths, and worst scores on general cognitive function, executive function, and attention/working memory tests.

Conclusion:

❖Our results replicated **Gao et al**'s associations between carotid rating, carotid length, SI volume, and cognition in both AD & SIV groups, indicating a dynamic interaction between cholinergic deficit and intracranial macrovascular disease.

Fig8a

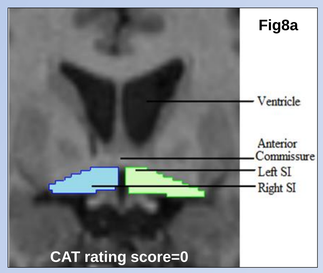
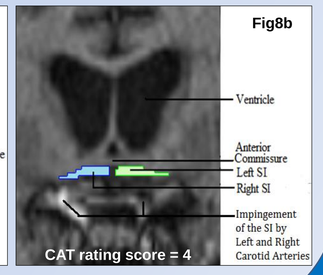


Fig8b



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Acknowledgements

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