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Visualization of atrophy of medial temporal lobes and the septal nuclei in patients with transient ischaemic attack and controls

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ABSTRACT

Introduction: Transient ischaemic attack (TIA) is associated with increased risk of cognitive decline and dementia as early as one-year post-event. Regional brain atrophy measurements may predict future cognitive decline. **Aims:** 1) To determine whether Medial Temporal Atrophy (MTA) scores and interseptal distance (ISD) measurements are greater in patients with TIA compared to controls; and 2) To determine whether MTA and ISD predicts cognitive change one year after TIA.
Methods: Baseline demographic, vascular risk factors, structural imaging and cognitive tests scores were compared between 103 Patients with TIA and 103 age-and-sex-matched controls from the Predementia Neuroimaging of Transient Ischaemic Attack (PREVENT) Study. MTA was assessed using the Schelten's Scale, and ISD was calculated as the distance between the septal nucleus of each hemisphere. Multiple linear regression models were used to evaluate how MTA and ISD related to cognitive change after adjusting for covariates.
Results: Patients with TIA had larger ISD measurements (1.4 mm [SD=1.2] vs. 0.9 mm [SD=1.0]); $p < 0.001$) and higher right/left MTA scores (both $p < 0.05$) compared to controls. At baseline, controls performed significantly better on the RAVLT (total recall), BVMT (total and delayed recall) and the Trail Making Task (A and B) compared to patients with TIA. However, at one-year follow-up there was no evidence of decline in the patients with TIA compared with controls. Higher MTA and ISD scores were not associated with cognitive decline.
Conclusions: Patients with TIA had higher MTA scores and ISD measurements than controls, but neither were predictors of cognitive decline at one year. Future studies with longer follow-up periods will be required to determine whether higher MTA scores and ISD predict risk of cognitive decline in patients with TIA.

Introduction

Transient ischaemic attack (TIA) is associated with an approximate 15–20% increase in the risk of ischaemic stroke after 5 years [1], and persistent cognitive impairment has been reported up to three months following the event [2–4]. Late-life cognitive impairment and dementia is most commonly related to the co-existence of two pathologies: Alzheimer's disease (AD) and small vessel disease [5]. Structural neuroimaging measures such as hippocampal and cerebral atrophy have been useful in monitoring and predicting cognitive decline in preclinical AD [6]. Recent work has found that TIA and minor stroke patients exhibit increased rates of cerebral atrophy compared to healthy controls [7], providing evidence of a preclinical dementia state in this population.

Unfortunately, the use of sophisticated magnetic resonance (MR) imaging techniques are not widely available in clinical practice due to

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logistical barriers such as the need for specialized hardware and long processing times. Visual rating scales such as Scheltens' medial temporal atrophy (MTA) scores [8] provide a practical, cost-effective alternative. Indeed, MTA scores have been found to predict the conversion from mild cognitive impairment (MCI) to dementia [9]. Larger MTA scores have been associated with global cognitive impairment one year after ischaemic stroke [10]. Additionally, the interseptal distance (ISD), or distance between adjacent septal nuclei, has recently been proposed as a practical measure of septal atrophy seen in AD, and has shown high sensitivity and specificity for distinguishing patients with and without memory impairment as well as MCI patients from controls [11] and so may be a valid marker of neurodegeneration. The clinical utility of these low-cost measures have not been thoroughly explored in the cont of predicting cognitive impairment in a TIA population.

Aims

The primary objectives of this study were to: (1) determine whether two easily accessible and low-cost measures, MTA and ISD, are greater in patients with TIA compared to controls; and (2) determine whether MTA and ISD are associated with cognitive decline over one year. We hypothesized that patients with TIA would have larger MTA scores and ISD measurements at baseline compared to controls, and that larger MTA and ISD at baseline would be associated with impaired cognition between baseline and follow-up across groups.

Material and methods

Participants

Participants for this study were enrolled in the Predementia Neuroimaging of Transient Ischaemic Attack (PREVENT) Study [12]. Patients with TIA were recruited from the Calgary Foothills Medical Center or Calgary Stroke Prevention Clinic between February 2015 and August 2019. Healthy controls were recruited through a combination of community flyers and spouses of patients with TIA. The study design and recruitment protocol for the PREVENT Study is depicted in Fig. 1. Briefly, the inclusion criteria for patients with TIA included: (1) first documented TIA defined by resolved symptoms (< 24 h) attributable to anterior circulation (motor, speech monocular vision loss) or posterior circulation (ataxia, diplopia, vertigo, hemi-weakness, hemianopia); (2) no dementia according to the National Institute of Aging-Alzheimer Association (NIA-AA) 2011 criteria [13]; (3) a clinical MR scan and cognitive testing within 10 days of TIA symptoms; (4) between the ages of 45 and 80 at recruitment; and (5) fluency in English. Inclusion criteria for healthy controls included: (1) no dementia according to the NIA-AA 2011 criteria [13]; (2) between the ages of 45 and 80 at recruitment; and (3) fluency in English. Exclusion criteria for both groups included: (1) other central nervous system disease, substance abuse, psychiatric illness, use of anti-psychotic medications or sedatives; and (2) contra-indication to MR brain scan (e.g., claustrophobia, pacemaker). None of the subjects met criteria for mild cognitive impairment (MCI), nor was there a history of delirium among participants at recruitment. All procedures for this study were approved by the University of Calgary Conjoint Health Research Ethics Board and all participants provided written informed consent prior to enrollment.

Clinical data

Framingham risk score

Vascular risk factors were amalgamated into a single Framingham risk score (FRS) which indicates an individual's 10-year risk of developing coronary artery disease [14]. Vascular risk factors were recorded and computed into the Framingham Risk Score (FRS) [14] and included: smoking, diabetes, total cholesterol, HDL cholesterol, systolic blood pressure (BP), medication for BP, and family history of cardiovascular disease. The FRS are expressed as a 3-point numerical from low to high risk value with higher scores reflecting higher vascular risk (MyHealth.Alberta.Ca).

Imaging acquisition

Participants underwent MR imaging at baseline using a 3.0T Diagnostic MR Scanner (General Electric Discovery 750). For this analysis, T1-weighted images and T2-weighted fluid-attenuated recovery (FLAIR) sequences were used. T1-weighted images were acquired using a 3D inversion recovery prepared spoiled gradient-echo sequence (3D; field of view (FOV) = 24 cm^2; one hundred and seventy-six 1.0 mm slice with a 0 mm gap; acquisition matrix = 256 × 256; TE = 2.932 ms; TR = 6.66 ms; flip angle = 8°; inversion time (TI) = 650 ms; phase FOV = 85%; reconstructed voxel size = 5392 mm isotropic). The 3D T2-weighted FLAIR sequence was acquired with an acquisition matrix size = 512 × 512; FOV = 24 cm; thirty-eight 1.0 mm slice with a 0 mm gap; TE = 81.7 ms, TR = 8000 ms, TI = 2198.1 ms, flip angle = 90°

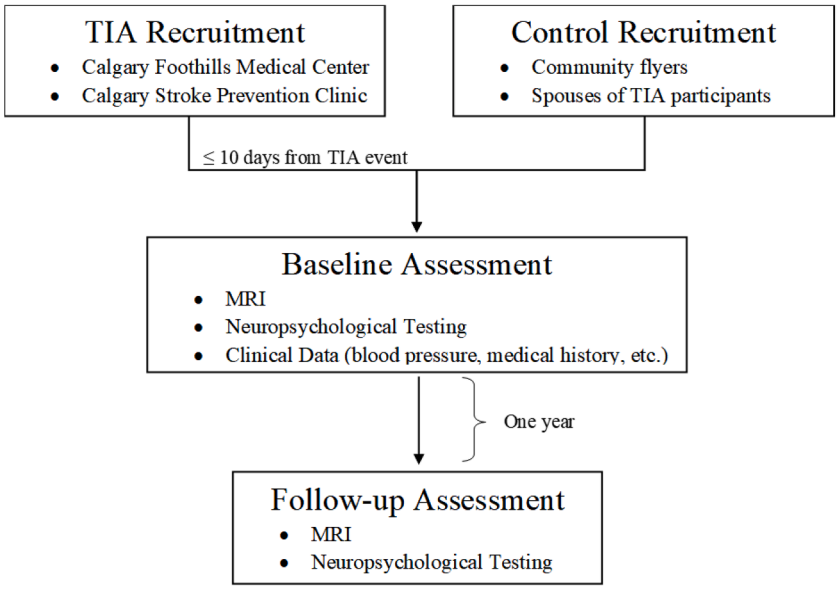

Fig. 1. Prevent study recruitment and study design.

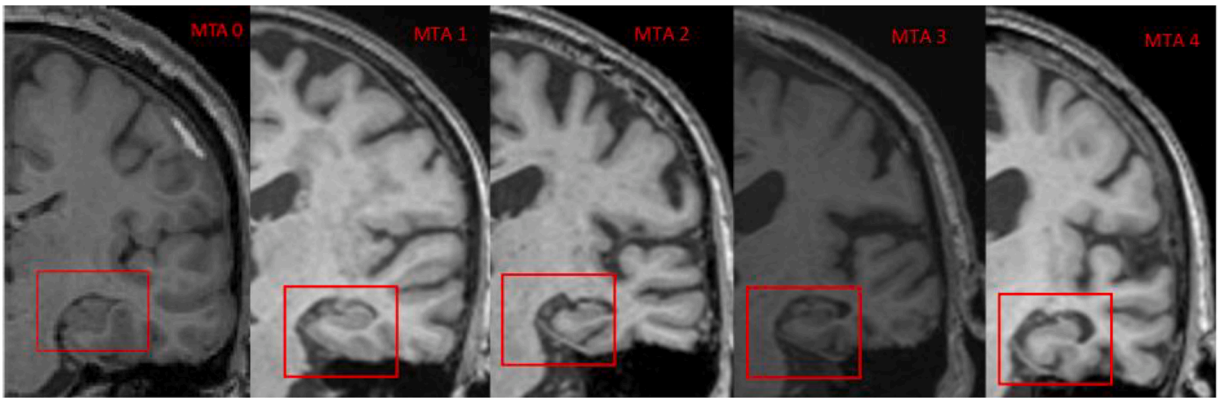

Fig. 2. Example medial temporal atrophy (MTA) scoring from zero to four, with higher numbers indicating greater atrophy.

Hippocampal and whole brain volume, white matter hyperintensities

Baseline brain volume (mm^3) was computed using SIENAX (Structural Imaging Evaluation Using Normalization of Atrophy, Cross-sectional) and was normalized to individual patient skull size. Left and right hippocampal volumes (mm^3) were calculated using FSL's FIRST function (sub-cortical structure segmentation tool) [15,16] (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Finally, white matter hyperintensity (WMH) volume (mL) was calculated based on the global threshold and contrast between different anatomical regions on the baseline FLAIR using the software Cerebra-WML [17]. All imaging metrics were corrected for age, sex, and normalized brain volume.

MTA scores

Medial temporal atrophy (MTA) scores for both the left and right hippocampi were visually assessed by an expert rater (PAB) on T1 images according to the methodology described by Scheltens et al. [8] Level of atrophy was ranked on a five-point scale (0–4) in order of increased atrophy (Fig. 2). Two additional raters (MJS and AA) rated MTA for 45 participants to determine inter-rater reliability.

Inter-septal distance

Inter-septal distance (ISD) is defined as the minimum distance between the septal nuclei of each hemisphere. In accordance with the methodology outlined by Gan and colleagues, [11] the distance between the medial convexities of the septal nuclei of each hemisphere, posterior to the anterior cerebral arteries, was used for this marker. This measurement was performed on T1 images by an expert neurologist (PAB). An example of an ISD measurement is shown in Fig. 3.

Neuropsychological assessment

All participants ($n = 206$) completed neuropsychological assessment at baseline, and around 133 (65%) of them completed all tests at 1-year follow-up. Four cognitive tasks were chosen for the current study to assess deficits in global cognition, verbal and visual episodic memory, processing speed, and executive function. The Montreal Cognitive Assessment (MoCA) was used as a brief cognitive screening test to measure of cognitive status. The Rey Auditory Verbal Learning Task (RAVLT) and the Brief Visuospatial Memory Task (BVMT) were used as measures of verbal and visuospatial memory respectively. The Trail Making Task parts A and B (TMT) and the Coding Task from the Wechsler Adult Intelligence Test Fourth Edition were used as measures of processing speed and executive function [18]. Alternate version of the MoCA, RAVLT, and BVMT were administered at one year to reduce learning effects. Additionally, the National Adult Reading Task (NART) and the Mini Mental State Examination (MMSE) were administered at baseline to determine premorbid verbal intelligence and cognitive status of each group at enrollment.

Statistical analysis

To correct for discrepancies in age and sex distribution between groups, participants were matched 1:1 for sex and age (with a leniency of two years difference allowed for age). Sample characteristics were compared between Patients with TIA and controls using Mann-Whitney U tests and Chi-square tests, for continuous variables and categorical variables, respectively. Spearman correlations were used to measure the relationship between MTA scores with hippocampal volumes and ISD measurements. Interclass correlations were used to determine the inter-

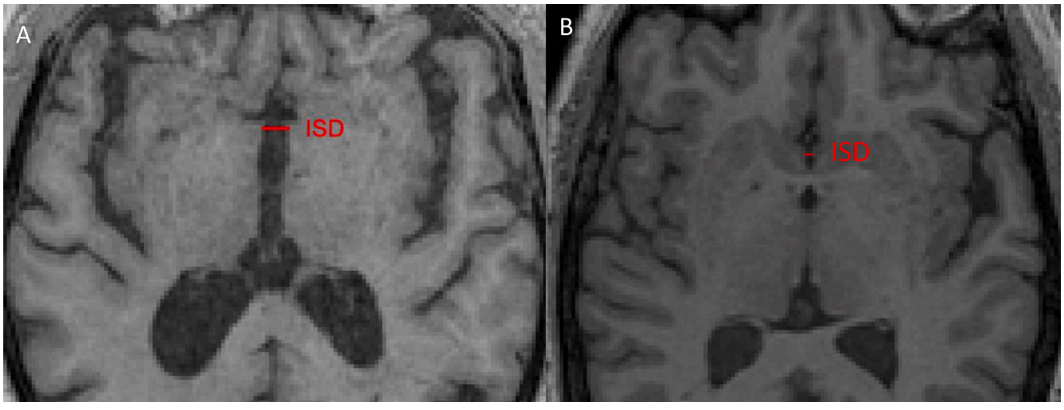

Fig. 3. The application of ISD measurement (mm) just posterior of the anterior commissure on two different participants with large (A, 4.1 mm) and shorter (B, 0.95 mm) ISD measures.

Table 1
Baseline demographic characteristics and neuroimaging.

	Missing N	Overall sample $N = 206$	TIA ($n = 103$)	Control ($n = 103$)	p values
Age, mean (SD)	0	65.2 (9.0)	65.4 (9.1)	65.1 (9.0)	.786
Sex (F/M), n	0	128/78	64/39	64/39	n/a
MMSE, mean (SD)	1	29.2 (1.3)	29.0 (1.4)	29.3 (1.2)	.019
Verbal Intelligence, mean (SD)	1	108.7 (9.3)	106.4 (10.1)	110.9 (8.0)	<0.001
FRS (1/2/3), n	1	61/68/76	21/33/49	40/35/27	.002
NBV (mm^3), mean (SD)	5	1456.5 (100.4)	1456.5 (89.7)	1456.6 (110.4)	.632
WMH Volume (mL), mean (SD)	2	5.3 (8.8)	6.4 (9.5)	4.2 (7.9)	.007
Right Hippocampus (mm^3), mean (SD)	3	3662.7 (489.5)	3628.6 (487.6)	3696.5 (491.4)	.346
Left Hippocampus (mm^3), mean (SD)	3	3583.7 (453.5)	3545.8 (465.1)	3621.2 (470.7)	.391
Right MTA (median, Q1-Q3)	2	1 (0–2)	1 (1–1)	1 (0–1)	.013
Left MTA (median, Q1-Q3)	2	1 (0–2)	1 (1–2)	1 (0–1)	<0.001
Right MTA $\geq$ 2, n (%)	2	53 (26.0)	35 (34.3)	18 (17.7)	.007
Left MTA $\geq$ 2, n (%)	2	56 (27.5)	39 (38.2)	17 (16.7)	.001
ISD (mm), mean (SD)	3	1.2 (1.2)	1.4 (1.2)	0.9 (1.0)	.001

Abbreviations: SD=standard deviations; Q1=first quartile; Q3= third quartile; TIA= Transient ischaemic attack; *F*=female; *M*=male; MMSE= the Mini Mental State Examination; NBV = normalized brain volume, MTA = medial temporal atrophy, FRS = Framingham risk score, ISD = interseptal distance, WMH=white matter hyperintensity.

Table 2
Baseline cognitive performance between TIA and Controls.

	TIA median (Q1-Q3)	Control median (Q1-Q3)	p-value
MoCA	26 (23–28)	27 (25–29)	<0.001
RAVLT Immediate Recall	10 (6–12)	11 (9–13)	.006
BVMT Total Recall	20 (15–25)	25 (17–28)	.002
BVMT Delayed Recall	9 (6–11)	10 (8–12)	<0.001
TMTA(s)	33 (27–42)	28 (23–36)	<0.001
TMTB(s)	75 (59–102)	65 (49–85)	.003
DS Coding	54 (47–67)	64 (52–74)	.002

The numbers reported were medians and first and third quartiles. MoCA = Montreal Cognitive Assessment, RAVLT = Rey Auditory Verbal Learning Test, BVMT = Brief Visuospatial Memory Test, TMT = Trail Making Test, DS = Digit Span; Q1=first quartile; Q3= third quartile.

Table 3
Change in cognitive performance over one year between TIA and Controls.

	TIA median (Q1-Q3)	**Control median (Q1-Q3)**	**p-value**
MoCA decline	−1 (−3–2)	0 (−2–2)	.170
RAVLT Immediate Recall decline	−1 (−3–0)	−2 (−3–0)	.114
BVMT Total Recall decline	−5 (−7–0)	−1 (−6–2)	.060
BVMT Delayed Recall decline	−1 (−2–0)	0 (−1–1)	.021
TMTA (s) decline	−2 (−5–6)	0.2 (−6 - 5)	.885
TMTB (s) decline	−4 (−13–10)	2 (−10–16)	.053
DS Coding decline	−2 (−10–5)	−1 (−6–3)	.630

We defined decline as baseline values - follow-up values for MoCA, RAVLT, BVMT total recall, BVMT delayed recall, and DS coding. We defined decline as follow-up values - baseline values for TMTA and TMTB. Therefore, a negative value indicates that the score was better at follow-up than baseline (i.e., that cognition improved). A positive value indicates that the score was worse at follow-up than baseline. Abbreviations: MoCA = Montreal Cognitive Assessment, RAVLT = Rey Auditory Verbal Learning Test, BVMT = Brief Visuospatial Memory Test, TMT = Trail Making Test, DS = Digit Span. Q1=first quartile; Q3= third quartile.

rater reliability of the MTA scores and ISD measurements. Baseline cognitive performance and cognitive decline between TIA and controls were compared using Mann-Whitney U tests. Multiple linear regression (MLR) models were used to test whether MTA and ISD scores were associated with baseline cognitive performance, with adjustment for age, sex, group status (TIA vs. control), premorbid IQ, FRS, normalized brain volume, and WMH. Similar analyses were conducted to examine how MTA and ISD associated with 1-year follow up cognition, with additionally for adjusting for corresponding baseline cognitive performance. In total, 24 MLR models were conducted. The statistical significance threshold was set at $\alpha = 0.05$ and analyses were conducted in SAS v9.4 (SAS Institute Cary, NC).

Results

A final sample of 103 Patients with TIA and 103 controls was achieved after matching. The median follow-up time (between baseline and follow-up assessment) was approximately 459 days (first and third quartile were 412 days and 511 days, respectively). Demographic and neuroimaging metrics are summarized in Table 1. Based on crude comparisons, patients with TIA presented with significantly higher FRS scores, WMH volume, and ISD; and significantly lower NART when compared with controls. Between baseline and follow-up, 10 participants did not complete one-year follow-up due to being unavailable, three participants died, four participants no longer met the inclusion criteria (e.g., being unable to complete an MRI scan due to new cardiac implant), 18 participants were unable to be contacted, two participants moved away, and 26 withdrew. The remaining missing data ($n = 26$) was the result of interruptions due to the COVID-19 pandemic.

We found positive correlation between ISD and MTA scores (spearman correlations: 0.43 for both left and right MTA with $p < 0.001$). The intra-class correlation coefficient (ICC) was computed to assess the agreement between two doctors in rating the MTA and ISD. A high degree of interrater reliability was found for the MTA scores. For the right MTA, average ICC = 0.85 ($F(44,44) = 7.03, p < 0.001$). For the left MTA, ICC = 0.77 ($F(44,44) = 4.78$, $p < 0.001$). There was good agreement between the ISD, using the two-way random effect models, ICC = 0.88 ($F(153, 153) = 18.0$; $p < 0.001$).

The cognitive test scores of TIA and control groups at baseline are presented in Table 2. Controls significantly outperformed patients with TIA on all measures of verbal and visual memory, processing speed, and executive function at baseline. For example, the median MoCA score was 26 [first and third quartiles (Q1-Q3): 23–28] for the TIA group and 27 (Q1-Q3:25–29) for the control group. The median of RAVLT immediate recall was 10 (Q1-Q3: 6–12) and 11 (Q1-Q3:9–13) for the TIA group and control group, respectively. Adjusting for the NART did not impact these differences. Counterintuitively, Table 3 shows that on average, most cognitive test scores did not decline at follow-up, particularly for the TIA group. From crude comparisons, there were no significant differences

Table 4
The relationship between Right MTA (2+ vs <2) and cognitive test at baseline, specifically memory (RAVLT, BVMT total, BVMT delay), and processing and executive function (including TMT A, TMT B, and DS). Models were adjusted for age, sex, NBV, NART, TIA v control, right hippocampal volume, WMH, and FRS based on multiple linear regression analyses.

	RAVLT ($N = 200$)	BVMT Total ($N = 200$)	BVMT Delayed ($N = 200$)	TMT A ($N = 200$)	TMT B ($N = 200$)	DS Coding ($N = 200$)
Right MTA 2+ vs <2	−0.39	−0.78	−0.33	1.10	6.99	−3.14
	[−1.43, 0.66]	[−3.08, 1.51]	[−1.23, 0.58]	[−4.89, 7.09]	[−7.71, 21.69]	[−7.76, 1.48]
TIA vs control	−0.78	−2.39 *	−1.14 **	4.73	9.62	−3.48
	[−1.73, 0.17]	[−4.47, −0.31]	[−1.96, −0.32]	[−0.69, 10.16]	[−3.70, 22.94]	[−7.66, 0.71]
Right hippocampal	−0.86	−0.50	−0.17	−1.58	3.63	2.69
	[−1.88, 0.17]	[−2.76, 1.75]	[−1.06, 0.72]	[−7.46, 4.31]	[−10.83, 18.08]	[−1.85, 7.23]
Age	−0.07 *	−0.26 ***	−0.09 **	0.36 *	1.83 ***	−0.42 **
	[−0.13, −0.00]	[−0.39, −0.12]	[−0.14, −0.03]	[0.00, 0.72]	[0.95, 2.71]	[−0.69, −0.14]
Sex: F vs M	1.21 *	0.03	0.16	1.55	−3.62	−3.18
	[0.06, 2.36]	[−2.50, 2.56]	[−0.84, 1.16]	[−5.06, 8.16]	[−19.85, 12.60]	[−8.28, 1.93]
NBV	2.55	1.57	1.65	−5.69	−29.09	5.95
	[−2.51, 7.61]	[−9.54, 12.69]	[−2.73, 6.03]	[−34.68, 23.30]	[−100.26, 42.07]	[−16.43, 28.32]
Premorbid.IQ	0.08 **	0.18 ***	0.09 ***	−0.15	−1.13 **	0.17
	[0.03, 0.12]	[0.08, 0.29]	[0.04, 0.13]	[−0.43, 0.12]	[−1.81, −0.45]	[−0.05, 0.38]
FRS: Moderate vs low	0.03	−1.36	−0.35	−0.17	−9.45	3.50
	[−1.15, 1.21]	[−3.94, 1.23]	[−1.37, 0.67]	[−6.91, 6.57]	[−26.01, 7.11]	[−1.71, 8.71]
FRS: High vs low	−0.68	−0.42	0.16	4.40	7.79	−6.28
	[−2.15, 0.79]	[−3.65, 2.81]	[−1.11, 1.43]	[−4.03, 12.82]	[−12.90, 28.48]	[−12.79, 0.22]
WMH	−0.03	−0.01	−0.02	0.16	0.68	−0.02
	[−0.09, 0.02]	[−0.14, 0.11]	[−0.07, 0.03]	[−0.17, 0.48]	[−0.12, 1.48]	[−0.27, 0.23]

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Table 5
The relationship between ISD and cognitive test at baseline, specifically memory (RAVLT, BVMT total, BVMT delay), and processing and executive function (including TMT A, TMT B, and DS). Models were adjusted for age, sex, NBV, NART, TIA v control, right hippocampal volume, WMH, and FRS based on multiple linear regression analyses.

	RAVLT ($N = 200$)	BVMT Total ($N = 200$)	BVMT Delayed ($N = 200$)	TMT A ($N = 200$)	TMT B ($N = 200$)	DS Coding ($N = 200$)
ISD	−0.42	−0.52	−0.19	1.41	0.01	−0.60
	[−0.85, 0.01]	[−1.47, 0.43]	[−0.56, 0.19]	[−1.07, 3.90]	[−6.11, 6.14]	[−2.53, 1.32]
TIA vs control	−0.64	−2.26 *	−1.10 **	4.23	10.70	−3.67
	[−1.59, 0.31]	[−4.36, −0.17]	[−1.93, −0.27]	[−1.23, 9.69]	[−2.78, 24.17]	[−7.92, 0.57]
Right hippocampal	−0.85	−0.46	−0.15	−1.56	2.80	3.00
	[−1.87, 0.16]	[−2.70, 1.77]	[−1.03, 0.73]	[−7.39, 4.27]	[−11.60, 17.20]	[−1.53, 7.53]
Age	−0.06	−0.25 ***	−0.08 **	0.33	1.86 ***	−0.42 **
	[−0.12, 0.00]	[−0.38, −0.11]	[−0.14, −0.03]	[−0.03, 0.69]	[0.97, 2.76]	[−0.70, −0.14]
Sex: F vs M	1.17 *	0.01	0.16	1.73	−4.37	−2.97
	[0.02, 2.31]	[−2.52, 2.53]	[−0.84, 1.15]	[−4.85, 8.31]	[−20.61, 11.87]	[−8.08, 2.15]
NBV	1.85	0.91	1.43	−3.21	−33.48	6.57
	[−3.22, 6.92]	[−10.30, 12.11]	[−2.98, 5.85]	[−32.40, 25.98]	[−105.53, 38.57]	[−16.11, 29.25]
Premorbid.IQ	0.08 **	0.18 ***	0.09 ***	−0.16	−1.14 **	0.17
	[0.03, 0.12]	[0.08, 0.29]	[0.05, 0.13]	[−0.43, 0.12]	[−1.82, −0.47]	[−0.04, 0.39]
FRS: Moderate vs low	0.10	−1.27	−0.32	−0.39	−9.52	3.62
	[−1.07, 1.27]	[−3.86, 1.31]	[−1.34, 0.70]	[−7.13, 6.34]	[−26.15, 7.10]	[−1.61, 8.86]
FRS: High vs low	−0.61	−0.30	0.21	4.18	7.05	−5.91
	[−2.06, 0.84]	[−3.52, 2.91]	[−1.06, 1.48]	[−4.20, 12.56]	[−13.63, 27.74]	[−12.42, 0.60]
WMH	−0.03	0.00	−0.01	0.13	0.67	−0.00
	[−0.08, 0.03]	[−0.13, 0.13]	[−0.06, 0.04]	[−0.20, 0.46]	[−0.14, 1.48]	[−0.26, 0.25]

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

between patients with TIA and controls with respect to changes in cognitive performance between baseline and follow-up except for the BVMT (delayed) where patients with TIA demonstrated significantly greater improvement compared to controls ($p = 0.02$).

Tables 4 and 5 shows that right MTA or ISD was not statistically significant associated with baseline cognitive scores, after consideration of right hippocampal volume, NBV, WMH, age, sex, premorbid IQ, TIA status, and FRS using multiple linear regression analyses. Table 6 shows that right MTA was also not statistically significant associated with 1-year cognitive scores at baseline, after adjusting for the corresponding baseline cognitive scores, hippocampal volume, NBV, WMH, age, sex, premorbid IQ, TIA status, and FRS using multiple linear regression analyses. Table 7 shows that ISD was associated with 1-year RAVLT scores, specifically, the estimated rate of change of 1-year RAVLT was 0.39 units per 1 unit increase of ISD, after considering other covariates besides baseline RAVLT score.

Discussion

This study has shown that patients with TIA have greater medial temporal scores and septal nuclei distance compared to age and sex matched controls when assessed using MTA scores and ISD measurements. However, the results of this study do not support the hypothesis that MTA and ISD are predictors of cognitive ability at one year. Consistent with previous findings, patients with TIA exhibited poorer cognitive performance immediately following TIA compared to controls [3,4,19] Patients with TIA on average exhibited improved cognitive raw scores as did controls to a lesser degree. These improvements are modest

Table 6
The relationship between Right MTA (2+ vs <2) and cognitive test at 1-year, specifically memory (RAVLT, BVMT total, BVMT delay), and processing and executive function (including TMT A, TMT B, and DS). Models were adjusted for baseline cognitive test, age, sex, NBV, premorbid IQ, TIA v control, right hippocampal volume, WMH, and FRS, based on multiple linear regression analyses.

	RAVLT (*N* = 132)	**BVMT Total (*N* = 132)**	**BVMT Delayed (*N* = 132)**	**TMT A (*N* = 132)**	**TMT B (*N* = 131)**	**DS Coding (*N* = 132)**
Right MTA 2+ vs <2	0.55 [−0.26, 1.35]	0.48 [−0.41, 1.36]	1.50 [−0.60, 3.59]	0.85 [−3.10, 4.80]	−6.46 [−16.42, 3.50]	−1.51 [−5.74, 2.72]
TIA vs control	−0.69 [−1.41, 0.03]	0.83 * [0.04, 1.62]	0.82 [−1.05, 2.70]	1.82 [−1.72, 5.36]	−7.23 [−16.29, 1.83]	1.83 [−1.97, 5.64]
Right hippocampal	0.08 [−0.74, 0.89]	−0.38 [−1.28, 0.51]	−0.96 [−3.09, 1.17]	−2.29 [−6.29, 1.71]	−10.38 * [−20.46, −0.30]	1.85 [−2.44, 6.15]
Age	−0.07 ** [−0.12, −0.02]	−0.05 [−0.11, 0.01]	−0.21 ** [−0.35, −0.07]	0.19 [−0.07, 0.45]	0.42 [−0.26, 1.10]	−0.04 [−0.32, 0.24]
Sex: F vs M	0.28 [−0.64, 1.19]	−0.88 [−1.87, 0.11]	−0.99 [−3.36, 1.37]	0.47 [−3.97, 4.91]	5.50 [−5.73, 16.73]	−1.49 [−6.24, 3.25]
NBV	−2.79 [−6.81, 1.22]	4.26 [−0.20, 8.73]	−4.24 [−14.71, 6.22]	−20.98 * [−40.83, −1.14]	2.31 [−47.54, 52.15]	5.59 [−15.51, 26.69]
Premorbid.IQ	0.02 [−0.02, 0.06]	0.04 [−0.00, 0.09]	0.09 [−0.01, 0.20]	0.08 [−0.11, 0.27]	−0.26 [−0.77, 0.25]	−0.01 [−0.21, 0.20]
FRS: Moderate vs low	−0.37 [−1.33, 0.58]	−0.04 [−1.09, 1.01]	0.03 [−2.46, 2.52]	−2.01 [−6.73, 2.71]	3.45 [−8.42, 15.33]	0.19 [−4.84, 5.21]
FRS: High vs low	−0.55 [−1.68, 0.59]	−0.48 [−1.72, 0.76]	−0.96 [−3.90, 1.99]	1.50 [−4.09, 7.09]	13.03 [−1.02, 27.08]	−0.76 [−6.77, 5.25]
WMH	0.03 [−0.02, 0.07]	−0.00 [−0.05, 0.04]	−0.09 [−0.20, 0.02]	0.15 [−0.07, 0.36]	−0.01 [−0.54, 0.53]	−0.11 [−0.34, 0.11]
RAVLT.Y0	0.50 *** [0.38, 0.61]					
BVMT.Y0		0.19 *** [0.14, 0.25]				
BVMT. Delay. Y0			1.54 *** [1.20, 1.88]			
TMTA.Y0				0.39 *** [0.24, 0.55]		
TMTB.Y0					0.61 *** [0.47, 0.75]	
DS. Y0						0.85 *** [0.69, 1.00]

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

and do not reflect clinically significant cognitive change (i.e., greater than 0.5 standardized difference). The greater improvement observed in patients with TIA (notably on the RAVLT and BVMT) may indicate that some process of recovery occurred that was captured between the two cognitive assessments. Additionally, a previous study has reported that global transient cognitive impairment is most frequent during the first seven days after TIA episode [19]. Thus, it is plausible that improved performance on measures of episodic memory were the result of natural improvements in the cognitive abilities of patients with TIA post event. It is well recognized that modest improvements on cognitive assessments do occur even when alternate forms of the test are used [20]. It is therefore also possible that practice effects contributed to the increase in scores on these tasks, although previous literature suggests small practice effects only at short intervals (<six weeks) on these measures [21–23], and the use of alternate forms would reduce this possibility.

Although patients with TIA had significantly larger MTA scores, the range of scores for both groups fell primarily between 0 and 2. Longer follow-up duration will determine whether MTA scores and ISD measurements, both of which can be easily implemented in a clinical setting, can be used to identify patients at greater risk of cognitive decline. Both left and right MTA scores strong interrater agreement, lending support for the use of MTA scores as a valid and reliable tool for assessing hippocampal atrophy. However, both left and right MTA scores were only weakly correlated with hippocampal volumetric analyses. This is consistent with a previous report finding significant but only weak to moderate correlations between visual MTA scores and hippocampal volume [24]. Thus, further investigation is warranted to determine if MTA scores are truly a valid replacement for sophisticated volumetric analyses in clinical settings.

At baseline, patients with TIA performed significantly worse on all neuropsychological assessments compared to age-matched controls, consistent with previous observations [25]. However, it is possible that these differences in baseline cognitive test scores between groups were driven by discrepancies in premorbid verbal intelligence and cognitive status, as controls performed significantly higher on the NART and MMSE compared to patients with TIA even after age and sex matching.

The reduced sample size after age and sex matching is a potential limitation to our study as this may have resulted in insufficient power to find significant results. However, matching our participants limited any confounding effects of between group age and sex discrepancies in our analyses. This is an important consideration as between group differences in age would make it difficult to interpret comparisons of cognitive findings between groups [26].

Due to the lack of decline in cognitive scores between baseline and follow-up assessment, we were unable to properly test our hypothesis that higher MTA scores and ISD at baseline would be associated with cognitive decline at one year and were unable to assess the clinical impact of these measures despite baseline differences between controls and TIA participants. It is possible that a one-year period was not sufficient time for noticeable cognitive decline to occur in patients with TIA and that a long follow-up period would be required to detect changes in cognitive function. Future studies may also wish to include other neuroimaging variables in prediction models such as perivascular spaces which have been found to be associated with cognitive decline one-year post-stroke/TIA in previous work [27].

Table 7
The relationship between ISD and cognitive test at 1-year, specifically memory (RAVLT, BVMT total, BVMT delay), and processing and executive function (including TMT A, TMT B, and DS). Models were adjusted for baseline cognitive test, age, sex, NBV, premorbid IQ, TIA v control, right hippocampal volume, WMH, and FRS, based on multiple linear regression analyses.

	RAVLT ($N = 132$)	**BVMT Total ($N = 132$)**	**BVMT Delayed ($N = 132$)**	**TMT A ($N = 132$)**	**TMT B ($N = 131$)**	**DS Coding ($N = 132$)**
ISD	0.39 * [0.05, 0.73]	−0.19 [−0.56, 0.18]	−0.09 [−0.98, 0.79]	−0.15 [−1.81, 1.51]	−2.26 [−6.52, 2.00]	0.60 [−1.18, 2.37]
TIA vs control	−0.83 * [−1.55, −0.10]	0.99 * [0.18, 1.80]	1.06 [−0.87, 3.00]	2.00 [−1.62, 5.62]	−6.66 [−16.01, 2.69]	1.34 [−2.54, 5.23]
Right hippocampal	0.11 [−0.68, 0.91]	−0.55 [−1.44, 0.34]	−1.30 [−3.42, 0.83]	−2.50 [−6.47, 1.47]	−9.94 [−19.96, 0.09]	2.35 [−1.91, 6.61]
Age	−0.08 ** [−0.13, −0.03]	−0.04 [−0.10, 0.02]	−0.20 ** [−0.34, −0.06]	0.20 [−0.07, 0.46]	0.46 [−0.23, 1.15]	−0.06 [−0.34, 0.22]
Sex: F vs M	0.29 [−0.61, 1.19]	−1.04 * [−2.03, −0.05]	−1.32 [−3.70, 1.06]	0.26 [−4.16, 4.68]	5.70 [−5.56, 16.96]	−0.98 [−5.70, 3.75]
NBV	−2.63 [−6.59, 1.33]	3.86 [−0.61, 8.33]	−4.98 [−15.54, 5.58]	−21.55 * [−41.42, −1.68]	2.65 [−47.34, 52.64]	6.92 [−14.20, 28.04]
Premorbid.IQ	0.02 [−0.02, 0.06]	0.04 * [0.00, 0.09]	0.10 [−0.01, 0.20]	0.08 [−0.11, 0.27]	−0.29 [−0.80, 0.22]	−0.01 [−0.22, 0.19]
FRS: Moderate vs low	−0.51 [−1.46, 0.44]	0.05 [−1.01, 1.12]	0.11 [−2.42, 2.64]	−1.93 [−6.70, 2.83]	4.17 [−7.85, 16.18]	−0.10 [−5.17, 4.98]
FRS: High vs low	−0.66 [−1.78, 0.45]	−0.51 [−1.75, 0.72]	−1.16 [−4.12, 1.80]	1.41 [−4.16, 6.99]	14.21 * [0.19, 28.23]	−0.61 [−6.59, 5.37]
WMH	0.02 [−0.02, 0.06]	0.00 [−0.05, 0.05]	−0.09 [−0.20, 0.03]	0.15 [−0.07, 0.36]	0.05 [−0.50, 0.59]	−0.12 [−0.35, 0.11]
RAVLT.Y0	0.52 *** [0.41, 0.63]					
BVMT.Y0		0.19 *** [0.14, 0.25]				
BVMT. Delay. Y0			1.55 *** [1.21, 1.90]			
TMTA.Y0				0.39 *** [0.24, 0.54]		
TMTB.Y0					0.60 *** [0.46, 0.74]	
DS. Y0						0.85 *** [0.70, 1.00]

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Conclusions

In summary, this study found that patients with TIA have early evidence of atrophy of the medical temporal structures and septal nuclei as determined by the application of the MTA score and ISD measurement which are easy and reliable to administer clinically. However, these measurements are not associated with change in cognition one year post event. Future studies will determine the clinical utility of both the MTA scores and ISD measurement in determining the risk of cognitive decline.

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Declaration of Competing Interest

We the authors of the manuscript titled “Visualization of Atrophy of Medial Temporal Lobes and the Septal Nuclei in Patients with Transient Ischaemic Attack and Controls.

” declare our interest in the article being published in CCCB.

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