Original Contribution

Transient Ischemic Attack Results in Delayed Brain Atrophy and Cognitive Decline

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Background and Purpose—Transient ischemic attack (TIA) initiates an ischemic cascade without resulting in frank infarction and, as such, represents a novel model to study the effects of this ischemic cascade and secondary neurodegeneration in humans.

Methods—Patients with suspected TIA underwent acute brain perfusion imaging, and those with acute ischemia were enrolled into a prospective observational study. We collected baseline and 90-day magnetic resonance imaging, including MP-RAGE (high-resolution T1 sequence) and cognitive assessment with the Montreal Cognitive Assessment. Brain morphometry and within patient statistical analysis were performed to identify changes between baseline and 90-day imaging and clinical assessments.

Results—Fifty patients with TIA with acute perfusion lesions were studied. All patients experienced a decrease in global cortical gray matter (P=0.005). Patients with anterior circulation TIA (n=31) also had a significant reduction in the volume of the pons (P<0.001), ipsilesional parietal lobe (P<0.001), occipital lobe (P=0.002), frontal lobe (P<0.001), temporal lobe (P=0.003), and thalamus (P=0.016). Patients with an anterior perfusion lesion on acute imaging also had a significant decrease in Montreal Cognitive Assessment between baseline and day 90 (P=0.027), which may be related to the volume of thalamic atrophy (R^2=0.28; P=0.009).

Conclusions—In a prospective observational study, patients with TIA confirmed by acute perfusion imaging experienced a significant reduction in global gray matter and focal structural atrophy related to the area of acute ischemia. The atrophy also resulted in a proportional decreased cognitive performance on the Montreal Cognitive Assessment. Further studies are required to identify the mechanisms of this atrophy. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.019276.)**

Key Words: atrophy ■ cognition ■ gray matter ■ ischemic attack, transient ■ perfusion imaging

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Secondary neurodegeneration induced by ischemia is well documented in animal studies, yet the clinical relevance of this phenomenon in human stroke is uncertain. Prolonged ischemic damage causes not only infarction but also results in secondary processes, such as vasogenic edema,[1] excitotoxicity,[2] remote atrophy,[3] selective neuronal loss, diaschesis, and microglial activation.[4] Thalamic atrophy is also a commonly observed effect of secondary neurodegeneration.[5,6] However, the clinical relevance of thalamic atrophy, particularly as it is usually remote to the topography of the acute ischemic region, is unclear. Secondary neurodegeneration and the impact of remote atrophy after stroke is a challenging phenomenon to study in humans because the primary infarction and initial edema followed by tissue contraction because of atrophy and necrosis affect the ability to reliability quantify tissue properties, such as volume or structure.[7] Therefore, the behavioral and functional effects of these secondary ischemic effects are not well described in humans because they are generally indistinguishable from effects due to the original infarction.

Transient ischemic attack (TIA) exists at the mild end of the ischemic continuum. A TIA is defined by current radiological and clinical criteria as the result of transient focal brain hypoperfusion which spontaneously improves (eg, because of spontaneous fibrinolysis of an occluded vessel) and does not result in infarction but is accompanied by concurrent focal or global disturbances of cerebral function lasting <24 hours.[8] The temporary tissue hypoperfusion in TIA may still initiate the biological ischemic cascade within the brain, leading to secondary neurodegeneration.[9] Thus, TIA may be the best human model in which to study the secondary

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neurodegenerative effects of ischemia in relative isolation, which is almost impossible to do when there is frank infarction in patients with stroke with persistent clinical deficits.

We hypothesized in a population of patients with TIA with confirmed acute cerebral blood flow disturbance that secondary neurodegeneration would be present in the form of delayed atrophy and that this would lead to delayed clinical effects, particularly affecting cognitive function and mood. Therefore, the present study was designed to identify if clinically and radiologically confirmed TIA resulted in global or remote atrophy (ie, outside the initial ischemic region) and to identify if this atrophy was related to cognitive or mood changes.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. Patients presenting to the rapid referral TIA service or emergency department at John Hunter Hospital, Newcastle, Australia, with first-ever transient neurological symptoms suggestive of TIA or minor stroke were prospectively assessed by a stroke neurologist. All definite and possible TIA cases underwent acute computed tomography perfusion (CTP). For adjudication, electronic medical records and imaging records of patients with indeterminate diagnoses were independently reviewed by 2 experienced stroke neurologists, and a final decision was made by consensus. Patients presenting with symptoms typical of TIA/stroke mimics, such as migraine with aura, seizures, acute confusional states, hypoglycemia, patients with symptoms related to known prior stroke, or patients with a known history of conversion disorder, were excluded from the study. If a patient had a hemispheric perfusion abnormality on CTP consistent with their clinical presentation of TIA, they were admitted to hospital, and informed consent for this study was sought. Patients with isolated brain stem ischemia or a premorbid status suggesting a mild cognitive disturbance were excluded from this study. Patients with soft TIA (eg, isolated dizziness, visual disturbance, or sensory disturbance), a history of TIA, or stroke or those with a diffusion-weighted imaging lesion on follow-up imaging were also excluded. Enrolled patients were asked to return for follow-up assessments and imaging 90 days after their study enrollment. Patients who were enrolled in the study underwent a magnetic resonance imaging (MRI) at 24 hours and 90 days. This study was approved by the institutional ethics committee, and all patients gave informed consent.

Clinical Assessments

Baseline clinical data recorded included demographics (age, sex), vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking history, prior stroke/TIA, and ischemic heart disease), clinical features, and premorbid modified Rankin Scale score. Study-specific assessments were also performed at 24 hours and 90 days and included the Montreal Cognitive Assessment (MoCA), the Fatigue Severity Scale, and the Depression, Anxiety and Stress Scale.

Imaging

Baseline non-contrast computed tomography, CTP, and computed tomographic angiographic images were acquired on a 320-slice Toshiba scanner (Toshiba Aquilion ONE; Toshiba, Tokyo, Japan). Whole-brain CTP data were acquired simultaneously with 50 mL of contrast agent (Ultravist 370; Bayer Healthcare, Berlin, Germany) injected at 6 mL/s followed by 50 mL of saline with acquisitions at 19 time points during 60 seconds, beginning 7 seconds after contrast injection.

MRI was performed on a 3-T scanner (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) at 24 hours and 90 days after TIA diagnosis. The 24-hour MRI included an axial isotropic diffusion-weighted imaging, time-of-flight magnetic resonance angiography, fluid-attenuated inversion recovery, and a high-resolution 1-mm isotropic T1-MP-RAGE (TR=2000 ms, TI=900 ms, FOV=256×256 mm^2, TA=4:24 minutes) and perfusion-weighted imaging. The 90-day MRI included an axial isotropic diffusion-weighted imaging, MP-RAGE, and arterial spin labeling sequence.

Imaging Analysis

Perfusion maps were processed using commercial software, MIStar (Apollo Medical Imaging Technology, Melbourne, VIC, Australia). Global arterial input function using the unaffected anterior cerebral artery and venous outflow function from a large draining vein (sagittal sinus) were selected. Deconvolution of the tissue enhancement curve and arterial input function was performed using a model-free singular-value decomposition with a delay and dispersion correction. Maps of cerebral blood flow, cerebral blood volume, delay time to peak of the residual function, and mean transit time were generated for analysis. A delay time >3 seconds was used to define the perfusion lesion.[10] Lesions were considered artefactual if they were small (<5 mL) and were not located in regions which were not be topographically related to the symptoms of the patients. Patients were also categorized based on vascular system affected by the ischemic changes into either anterior or posterior circulation origin.

Data from the MP-RAGE protocol were processed with the fully automated segmentation MorphoBox prototype[11,12] to compute absolute volumes of the following brain tissue and structures: total intracranial volume, global and lobar gray and white matter, thalamus, caudate, pallidum, putamen, pons, medulla oblongata, mesencephalon, insula, and cerebellum. It is important to note that the MorphoBox segmentation tool was used with the default parameter settings, and no manual editing was applied at any stage of the segmentation process. All segmentation processing was undertaken independently from the study staff at an external site (by M.B.), and results were visually inspected by an experienced observer for gross segmentation errors.

Healthy Control Comparison

Twenty healthy health controls were recruited from the community through a healthy volunteer registry and were matched to the TIA cohort based on age and number of vascular risk factors (including smoking status, history of diabetes mellitus or none, hypertension status, and statin or anticoagulant medication). All healthy controls never had a stroke or TIA in the past and did not have a family history of stroke or TIA. The healthy controls were screened for vascular risk factors, personal and family history of TIA/stroke before enrollment. Therefore, the healthy controls were recruited to have similar vascular risk factors as the patients with TIA enrolled in this study but never have had a TIA or stroke. The healthy controls underwent a single MRI assessment using the exact same sequences as the patients with TIA as a comparison group. The purpose of these single time point control image assessments was to compare the absolute brain volumes to our TIA cohort's brain volumes at both baseline and 90 days as an external validation method, as opposed to the within patient volume measurements over time.

Statistics

Baseline clinical assessments were analyzed with summary statistics and presented as mean with SD. In patients with TIA, we compared baseline and 90 days MP-RAGE volumes as a within patients using paired sample *t* tests and controlled baseline and 90-day TIA patient MP-RAGE–derived volumes to the controls using *t* test with data presented with a mean and SD. TIA patients brain volumes derived from the MP-RAGE at baseline and 90 days were also compared with the control patients MP-RAGE brain volumes using *t* tests. Baseline and 90-day clinical assessments were also compared within patients using paired sample *t* tests and presented with a mean and SD. Next, patients were dichotomized by the site of their baseline perfusion imaging as having either an anterior circulation or posterior circulation abnormality. Repeated paired sample *t* tests were performed with bootstrapping on the MRI T1-MP-RAGE data and clinical assessments to adjust for multiple comparisons, and all reported *P* values

represented analysis after bootstrapping. Linear regression was performed, and the R^2 reported to measure the influence of variables known to influence brain volume and extent of atrophy, such as age and sex.

Correlation analysis was performed to identify if there was a significant relationship between the extent of any changes seen between baseline and 90-day MRI T1-MP-RAGE in patients with TIA and the extent of changes measured on the clinical assessments (MoCA, Fatigue Severity Scale, and Depression, Anxiety And Stress Scale). If there was a significant correlation between imaging change and clinical assessments, linear regression was performed and an R^2 value reported. The correlation analysis was also repeated after dichotomization by vascular origin of the clinical symptoms at baseline, and if there were any significant correlations, a linear regression was performed to confirm the result and the R^2 value reported. All statistical analyses were performed using STATA (version 14, StataCorp LP, TX).

Results

Eighty-two patients with a clinical diagnosis of TIA were screened. Patients with clinical diagnosis of TIA but normal CTP or small CTP lesions deemed artefactual (21), incomplete baseline clinical data (2), incomplete imaging data (3), or who were lost to follow-up (6) and were excluded from the study. Of the 50 remaining patients with TIA who had a CTP lesion at baseline, mean age was 65 years (range, 37–94 years), and 36% (18) were women. The median time from symptom onset to hospital presentation was 147 minutes (interquartile range, 92–186 minutes), and the mean ABCD^2 score was 5. The 90-day MRI scan occurred a median of 91 days after acute TIA admission (range, 87–99 days), and no patients experienced a new stroke or TIA during the follow-up period. Patients reported symptom duration for 1 hour (range, 30 minutes–4 hours). Further description of the cohort is provided in Table 1. No enrolled patient with TIA had an abnormal perfusion imaging scan at 24 hours (with perfusion-weighted imaging) or 90 days (with arterial spin labeling), and at 90 days, no enrolled patients had any evidence of a new lesion on MRI. The control patients were well matched for age and presence of vascular risk factors (TIA age mean, 65 years; range, 37–94 years; control age mean, 59 years; range, 42–88 years; P=0.492).

Of the 50 patients with TIA, 19 (38%) had a clinical deficit and acute perfusion lesion in the posterior circulation and 31 (62%) in the anterior circulation. Of the 31 patients with an anterior circulation perfusion lesion, 12 (24% of all study patients) were in the right hemisphere and 19 (38% of all study patients) were in the left hemisphere. A significant computed tomography angiography abnormality was found in 14 (28%) patients, of whom 9 (64%) were considered to have clinically relevant large-vessel occlusive disease (based on anatomic location and clinical symptoms, 10 [71%] were extracranial, 9 [29%] intracranial). At baseline, there were no significant differences between TIA patients brain volumes and the control participants brain volumes (P>0.05).

Patients With TIA

A significant reduction in global cortical gray matter was observed in the patients with TIA between baseline and 90-day imaging (bootstrapped P=0.005; Table 2). Patients with TIA also had a significant reduction in global cortical gray matter at day 90 compared with the controls (bootstrapped P<0.001). There was also a significant reduction in the volume of the occipital lobes seen within all patients with TIA between baseline and 90-day imaging (bootstrapped P=0.01; Table 2) and significant reduction in the volume of the occipital lobes between patients with TIA at 90-day imaging and the control patients (bootstrapped P=0.008).

Anterior Circulation TIA

In the patients with an acute perfusion lesion in the anterior circulation, there was a significant reduction after bootstrapping between baseline and 90-day imaging of the volume of pons (P<0.001; Table 3), ipsilesional parietal lobe (P<0.001), ipsilesional occipital lobe (P=0.002), ipsilesional frontal lobe (P<0.001), ipsilesional temporal lobe (P=0.003), and ipsilesional thalamus (P=0.016). No significant interaction was seen between the presence of a computed tomography angiography-detected large-vessel occlusive disease and the degree of atrophy (P>0.05).

Posterior Circulation TIA

In patients with an acute posterior circulation perfusion lesion, there was a significant reduction in the volume of the

Table 1. Patient Characteristics

Baseline Characteristic	All Patients, n=50	Anterior Circulation Patient n=31	Posterior Circulation Patients n=19	*P* Value Between Anterior and Posterior Circulation Groups
Age, y, mean (SD)	65 (12)	67 (12)	62 (13)	0.716
Systolic blood pressure, mean (SD)	152 (19)	150 (15)	155 (25)	0.873
ABCD^2 score, mean (SD)	5 (1)	5 (1)	7 (1)	0.067
Diabetes mellitus, n (%)	11 (22%)	30%	7%	<0.001
Hypertension, n (%)	34 (68%)	74%	57%	0.197
Dyslipidemia, n (%)	22 (44%)	48%	36%	0.469
Smoker, n (%)	11 (22%)	4%	21%	0.037
Prior AF, n (%)	11 (22%)	13%	7%	0.021
Baseline CTP lesion volume, median (interquartile range)	8.7 mL (5–12.8 mL)	7.4 mL (5–13.2 mL)	9.6 mL (5.7–15.3 mL)	0.097
MoCA score at 24 h, mean (SD)	26 (3)	26 (4)	26 (3)	0.589

AF indicates atrial fibrillation; CTP, computed tomography perfusion; and MoCA, Montreal Cognitive Assessment.

Table 2. Volume Changes

Region	All Patients, Volumes n=50			
	Baseline Volume (mL, SD)	90-Day Volume (mL, SD)	% Change Between Time Points	*P* Value Between Time Points
Global gray matter	642.7 (61.1)	604.7 (83.5)	7% reduction	0.005
Global white matter	429.1 (63.1)	402.2 (50.9)	7% reduction	0.333
Ipsilesional parietal lobe	213.8 (24.1)	200.8 (69.1	6% reduction	0.258
Ipsilesional occipital lobe	87.9 (14.4)	81.4 (27.8)	8% reduction	0.01
Ipsilesional frontal lobe	306.5 (42.7)	301.2 (55.1)	2% reduction	0.779
Ipsilesional temporal lobe	176.1 (18.1)	165.3 (26.1)	7% reduction	0.251
Ipsilesional thalamus	13.4 (1.3)	12.2 (2.9)	10% reduction	0.065
Ipsilesional caudate	9.1 (1.6)	8.5 (2.8)	7% reduction	0.209
Ipsilesional putamen	13.7 (1.4)	12.6 (2.7)	9% reduction	0.13
Ipsilesional pallidum	3.7 (0.5)	3.5 (0.9)	6% reduction	0.518
Pons	15.5 (1.6)	14.8 (3.1)	5% reduction	0.38

ipsilesional occipital lobe over time (bootstrapped *P*=0.037; Table 4) but not in other measured structures.

Using linear regression, age was not significantly associated with global gray matter volume change within patients with TIA (R^2, 0.039; *P*=0.238). Other variables were also not significantly related to the extent of global gray matter decrease seen within patients with TIA, such as the volume of the perfusion lesion on admission imaging (R^2, 0.011; *P*=0.586), TIA symptom duration (R^2, 0.005; *P*=0.835), and sex (R^2, 0.107; *P*=0.725). Indeed, the volume of the acute CTP lesion (median, 8.7 mL; interquartile range, 5–12.8) was considerably smaller than the extent of observed atrophy (Tables 1 and 2). All physiological values were internally validated because there was no significant change in total intracranial volume over time (*P*=0.816), indicating that the results were because of pathology (atrophy) rather than segmentation errors.

Cognitive Effects

At 90 days, in the overall 50 patient TIA cohort, there was no significant decline in the MoCA (*P*=0.371; Table 4), Depression, Anxiety and Stress Scale (*P*=0.778), or Fatigue Severity Scale (=0.829) from baseline. However, in patients with an anterior circulation TIA, there was a significant decrease in MoCA between baseline and day 90 (*P*=0.027), specifically with impairments in the visuospatial and executive assessment (*P*=0.012), the attention score (*P*=0.036), and the orientation score (*P*=0.013). Last, linear regression identified that the MoCA change was significantly related to thalamic volume change between baseline and 90-day assessments (R^2=0.28; *P*=0.009) in all patients, with no other brain region being significantly related to the MoCA change (*P*>0.05). The association between thalamic atrophy and cognitive decline was also seen in the subgroup with anterior circulation perfusion lesions (R^2=0.21; *P*=0.039), indicating that

Table 3. Brain Volume Changes in Patients With TIA

Region	Anterior Circulation Patient n=31				Posterior Circulation Patients n=19			
	Baseline Volume (mL, SD)	90-Day Volume (mL, SD)	% Change Between Time Points	*P* Value Between Time Points	Baseline Volume (mL, SD)	90-Day Volume (mL, SD)	% Change Between Time Points	*P* Value Between Time Points
Global gray matter	640.8 (71.5)	601.1 (70.6)	7% reduction	<0.001	645.9 (40.9)	599.4 (74.3)	8% reduction	0.043
Global white matter	467.3 (57.1)	412.4 (61.4)	13% reduction	<0.001	418.3 (35.1)	386.4 (46.1)	5% reduction	0.452
Ipsilesional parietal lobe	218.1 (26.7)	211.1 (27.9)	3% reduction	<0.001	218.2 (19.2)	192.4 (29.5)	13% reduction	0.127
Ipsilesional occipital lobe	87.5 (17.3)	83.7 (16.1)	5% reduction	0.002	88.5 (7.9)	79.5 (12.3)	11% reduction	0.037
Ipsilesional frontal lobe	328.2 (49.2)	302.1 (47.7)	9% reduction	<0.001	313.8 (33.2)	296.9 (70.6)	6% reduction	0.24
Ipsilesional temporal lobe	179.1 (20.1)	174.6 (22.9)	3% reduction	0.003	178.5 (14.7)	162.6 (23.1)	10% reduction	0.15
Ipsilesional thalamus	13.3 (1.4)	11.1 (1.3)	14% reduction	0.016	13.6 (1.1)	11.8 (4.1)	10% reduction	0.096
Ipsilesional caudate	9.1 (1.4)	9.2 (1.5)	1% increase	0.046	9.2 (2.3)	8.4 (3.8)	10% reduction	0.14
Ipsilesional putamen	13.6 (1.6)	13.7 (1.7)	1% increase	0.602	13.7 (2.3)	12.9 (6.5)	6% reduction	0.121
Ipsilesional pallidum	3.6 (0.5)	3.8 (0.4)	5% increase	<0.001	3.7 (0.5)	3.6 (1.2)	3% reduction	0.218
Pons	15.7 (1.5)	15.2 (1.6)	3% reduction	<0.001	16.1 (1.4)	15.4 (3.7)	5% reduction	0.191

Table 4. Cognitive and Mood Changes

	All Patients, n=50			Anterior Circulation Patient n=31			Posterior Circulation Patients n=19		
Score	Baseline	Day 90	*P* Value Between Time Points	Baseline	Day 90	*P* Value Between	Baseline	Day 90	*P* Value Between Time Points
MoCA total	26.5	25.5	0.371	27	23.5	0.027	27	27	0.394
MoCA executive function	4.5	3.5	0.005	4.5	3.5	0.012	4.5	4	0.22
MoCA naming	3	3	0.16	3	3	0.162	3	3	0.947
MoCA attention	5.5	4.5	0.046	5.5	4	0.036	5.5	5.5	0.586
MoCA language	3	2	0.213	2.5	2	0.057	2.5	2.5	0.082
MoCA abstraction	2	2	0.136	2	2	0.295	2	2	0.166
MoCA delayed recall	3	2	0.475	3	2.5	0.221	2	2	0.57
MoCA orientation	6	5	0.017	6	4.5	0.013	3	3.5	0.339
FSS	3	3	0.829	3	3	0.442	6	6	0.688
DASS	18	17	0.778	17.5	16	0.785	19	19	0.993
DASS depression	4	5	0.616	4	4	0.976	3.5	5.5	0.407
DASS anxiety	5.5	5	0.537	5	5	0.795	3.5	3	0.412
DASS stress	9	8	0.463	8	7	0.615	1.5	1.5	0.6

DASS indicates Depression, Anxiety And Stress Scale; FSS, Fatigue Severity Scale; and MoCA, Montreal Cognitive Assessment.

the cognitive change was related to thalamic atrophy remote to the acute ischemia.

Discussion

We have identified that patients with a first-ever clinical diagnosis of TIA confirmed by acute perfusion imaging have significant delayed reduction in global gray matter volume, as well as significant delayed atrophy in focal cerebral regions, with the location of atrophy being partly dependent on the acutely affected circulation (anterior or posterior). Indeed, the extent of the tissue loss was large at ≈7%. In addition, we have shown that patients with a TIA affecting the anterior circulation experience remote atrophy of the thalamus in the order of 10% at 3-month post-TIA and that this results in reduced cognitive performance on the MoCA by a mean of 3.5/30 points (or 11%) for 3 months. We have also shown that commonly associated markers of atrophy, such as age, were not significantly related to the extent of atrophy seen in our TIA cohort; however, we are unable to make assertions as to whether these variables predict the occurrence of atrophy because all patients in our strictly clinically and radiologically defined TIA cohort experienced significant atrophy. Moreover, the atrophy seen in our TIA cohort occurred for a 90-day period which is rapid and can be explained by the acute ischemic insult driving the atrophy; however, we are also unable to identify when the majority of this atrophy occurred during the 90-day period because of the sampling of our cohort. These findings confirm the hypothesis that TIA results in significant brain atrophy and suggest that TIA is a novel and appropriate human model in which to study the secondary effects of ischemia, which might include potential interventions to prevent secondary neurodegeneration.

Patients with an anterior circulation TIA experienced widespread ipsilesional atrophy affecting critical regions involved in functional connections to multiple brain regions, such as the thalamus. The reduction in cognitive performance required a sensitive assessment (the MoCA) which is not usually performed as part of routine clinical assessment. This point is critical because it demonstrates that the cognitive effects of secondary neurodegeneration are subtle (at least in the short term) and would easily be missed or challenging to distinguish from the primary infarct if we were examining a poststroke population with large acute infarcts. Moreover, the atrophy seen in this study was significant but again required a specific assessment on MRI (thin-slice T1 imaging) which is not performed routinely in clinical practice. The clinical assessments used in this cohort study identify that routine clinical and imaging assessments are not sensitive nor specific enough to detect cognitive change after TIA and thus as clinicians we may not be documenting the more subtle and delayed effects of ischemia in this important patient group.

Apart from thalamus and pons, atrophy after TIA was restricted to the vascular regions affected by the TIA and was not detectable in contralateral brain regions. The current study used perfusion imaging to enroll patients with definite evidence of acute ischemia associated with the presence of clinical symptoms suggestive of a TIA and therefore is reporting on a cohort with a high rate of perfusion abnormalities in comparison to other studies, which may skew our enrolled patient population to the more severe end of the TIA spectrum. Inclusion of patients with purely clinically defined TIA would have run a high risk of TIA mimics being included in the analyses and diluting any atrophy observed in the current patient cohort. The evidence of a perfusion lesion and the focal nature of the observed atrophy suggests that the mechanism of action for the observed atrophy may be predominately a focal phenomena triggered by the initial hypoperfusion. Thus, the mechanisms of this focal secondary neurodegeneration may include delayed apoptosis, inflammation, and blood–brain barrier permeability changes. Such blood–brain barrier changes after ischemia

are a well-documented process and may facilitate neutrophil infiltration and microglia activation/deactivation, which then could promote atrophy. Further studies are required to identify if blocking blood–brain barrier leakage, delayed apoptotic processes, or neuroinflammatory processes after ischemia are able to prevent secondary neurodegeneration and may explain the atrophy we have observed.[13,14] However, the atrophy was much more extensive than the volumes of the original perfusion lesions, with extensive involvement in ipsilateral structures. Interestingly, 28% of the studied population showed signs of large-vessel occlusive disease, yet the interaction between computed tomography angiography findings and the extent of atrophy was not significant; however, this is likely because of the small absolute numbers studied. This may still be an effect of the initial ischemic process triggering the above mechanisms or may also relate to disconnection of perilesional regions because of structural (eg, fiber tract loss) or functional changes (eg, changes in neurotransmitter balance) incited by the original ischemic event. Last, TIA has been suggested to precondition the brain against ischemic stroke and result in a lower lesion volume in patients have are known to have had a TIA before their stroke.[15] Although this study has observed significant atrophy and cognitive worsening after TIA, this may be protective against more significant events later on in time.[16,17]

Although the MoCA results indicated no overall change in the cognitive status between time points, subgroup analysis of the anterior circulation ischemia group did show a decline in the MoCA score over time. This in turn appeared to be related to remote thalamic atrophy which has been previously reported.[5,6] Although subgroup analysis should always be interpreted with caution, we think there is a valid pathophysiological explanation for this in that the anterior circulation supplied brain in particular frontal lobes have extensive connections with the thalamus and the frontothalamic connections are crucial for normal cognitive functioning. The thalamic atrophy was more prominent in the anterior circulation TIA patients and well outside the original territory affected by acute ischemia. This likely indicates retrograde or anterograde degeneration (either structural or functional) between the originally affected ischemic region and these remote regions, which obviously have multiple connections with many parts of the brain. Further work is required to determine whether this remote atrophy does indeed reflect fiber loss between the regions and is related to changes in excitatory versus inhibitory neurotransmitter balance post-ischemia. Again, because the thalamus is a major highway connecting many parts of the brain, it is not surprising that the remote thalamic atrophy correlated with delayed cognitive decline.

Some study limitations need to be recognized. This is a single-center study of a highly selected patient population (all with acute perfusion abnormalities). This limits generalizability to the broader group of patients with clinically diagnosed TIA. However, this study was deliberately designed to exclude TIA mimics, of which there are many in a general population with a clinical diagnosis of TIA, as the clinical diagnosis alone of TIA is challenging and has poor interrater reliability.[18,19] Patients with a prior history of TIA were deliberately excluded because we were uncertain whether this may have confounded individual patients baseline and follow-up morphometry. In particular, previous TIA may be neuroprotective[15,16] and would be worthwhile of investigating if such patients have less atrophy from recurrent TIA. Moreover, the timing of the early MRI scan at 24 hours may have overestimated some brain volumes because of edema. However, the wide spread and consistent nature of the results and the minor impact of TIA indicate that any potential over estimation may be small. Next, the analysis with the MoCA did not take into account baseline education level of the patients or the extent of white matter hyperintensity volume or lesion load which are known to modify cognitive performance. Another issue to highlight is the multiple comparisons, by necessity, numerous hypothesis tests were performed, each at an α of 0.05, which will increase the probability of false-positive findings. However, we performed Bonferroni corrections and bootstrapping and observed that all the effects were in the expected direction (decreases in volume and function) and so are unlikely to be false positives. Furthermore, the imaging techniques and postprocessing used are readily available and well validated although the use of CTP to aid in diagnosis TIA is not currently standard of care. This study used internal validation through repeated scanning of patients with TIA, as well as external validation by recruiting matched controls to both assess and control for any measurement error. The minimal measured nonsignificant change in total intracranial volume (to volume within the skull) also validates the use of this studies imaging techniques. Last, this study did not observe any changes in mood and may be because this study was underpowered to make such observations if a change in mood because of TIA was to be expected.

In conclusion, we have demonstrated that a patient population of first-ever clinically and pathophysiologically confirmed TIA may be the ideal case mix in which to study secondary neurodegeneration after acute ischemia. We have shown that patients with TIA experience significant delayed atrophy remote of the acute ischemic region and that this resulted in delayed cognitive decline. Further studies are required to identify the exact mechanism of the atrophy and to possibly identify therapeutic targets for treatment aimed to prevent delayed atrophy and cognitive decline after stroke or TIA.

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Dr Bivard performed conception and design of the study, acquisition and analysis of data, and drafting the article and figures. Dr Krishnamurthy performed acquisition of data and drafting the article. Dr Lillicrap performed acquisition of data and drafting the article. Dr Maréchal performed analysis of data and drafting the article and figures. Dr Garcia-Esperon performed acquisition of data and drafting the article. Dr Holliday performed analysis of data and drafting the article and figures. Dr Levi performed conception and design of the study and drafting the article and figures. Dr Parsons performed conception and design of the study, analysis of data, and drafting the article and figures.

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Disclosures

None.

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