

RESEARCH PAPER

Progression of cognitive impairment in stroke/TIA patients over 3 years

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ABSTRACT

Objectives To examine how cognitive deficits progress in the years following a stroke or transient ischaemic attack (TIA).

Methods A follow-up study, with neuropsychological and MRI assessments undertaken 3 years after baseline assessments made 3–6 months poststroke in 183 stroke/TIA patients and 97 healthy controls participating in the Sydney Stroke Study. Additional measures included cardiovascular risk factors and apolipoprotein E (*APOE*) genotype.

Results Stroke/TIA patients had poorer cognitive function and more vascular risk factors than controls at baseline, but did not show greater decline in cognitive function over 3 years except for verbal memory. Patients with a subsequent stroke/TIA showed greater decline in global cognitive function and a number of domains. Rates of incident dementia were 5.9% per year in patients and 0.4% in controls. Both groups showed increased atrophy of the hippocampus, amygdala and whole brain, and an increase in white matter hyperintensities over 3 years; whole brain atrophy was greater in patients. Cognitive decline was greater in women and in those with smaller hippocampi at baseline. For patients without a subsequent stroke/TIA, those with smaller hippocampi or the *APOE* $\epsilon 4$ allele had greater global cognitive and verbal memory decline. **Conclusions** In poststroke patients, cognitive decline was not greater than in comparison subjects, except for verbal memory, unless they had another stroke/TIA. However, dementia incidence was higher in patients, as might be expected from their poorer baseline cognitive functioning. Smaller hippocampi were associated with an increased risk of decline in memory, and *APOE* $\epsilon 4$ was a risk factor in those without a subsequent stroke/TIA.

INTRODUCTION

Nearly one in four stroke patients has cognitive impairment severe enough to be diagnosed as dementia,^{1,2} and another one in three has milder levels of cognitive impairment.³ While some patients may show recovery over an extended period,⁴ an overall decline in cognitive function is to be expected.^{5–10} This is because stroke patients are at increased risk of further cerebrovascular events¹¹ and have a heavy burden of often progressive white matter (WM) lesions.¹² Vascular disease also increases the risk of Alzheimer-type pathology.¹³

Studies examining the progression of cognitive impairment in stroke patients have reported mixed results, largely due to sampling and methodological differences.^{4–10} While earlier studies suggested that

mortality rates were higher for vascular dementia (VaD) than Alzheimer's disease (AD),¹⁴ the rate of cognitive decline in VaD appears to be slower than AD.¹⁵ This is supported by the placebo arms of cholinesterase inhibitor trials in VaD.^{16–18} What happens to poststroke patients with only mild impairment over the longer term is less well studied, especially in the absence of further strokes or transient ischaemic attacks (TIAs).

We have previously reported that stroke/TIA patients in the Sydney Stroke Study exhibited mild declines in cognitive functions at 1 year after baseline.¹⁹ Decline was related to white matter hyperintensities (WMHs) and accentuated if a further cerebrovascular event occurred; education played a protective role. These patients were followed for a further 2 years to examine if a similar pattern of decline continued, and if the predictors of decline showed any change.

METHODS

Participants

Patients with a recent ischaemic stroke/TIA were recruited consecutively to the Sydney Stroke Study from two teaching hospitals affiliated with the University of New South Wales. Individuals were excluded if diagnosed with dementia or other neurological disorder prior to the stroke/TIA, had severe aphasia limiting assessment or were unable to consent to participate. Healthy controls were unpaid volunteers of similar age and from the same neighbourhood as the patients; they had no history of stroke/TIA, or other neurological or psychiatric disorder. Recruitment occurred over a 38-month period between May 1997 and June 2000. From a total of 1050 patients screened, 252 were considered eligible and recruited. There were also 129 controls recruited.

From all participants initially recruited to the Sydney Stroke Study, the present study included only those with neuropsychological and/or MRI data for one or both of baseline and 3-year follow-up assessments. After excluding five controls reporting a stroke/TIA between baseline and follow-up, neuropsychological data were available for 183 patients and 95 controls. MRI data were available for 117 patients and 79 controls (two controls provided MRI data only). There was more data available at baseline than at follow-up, with the reasons why follow-up data were unavailable including withdrawal from the study for 55 patients (68%) and 18 controls (78%), death for 21 patients (26%) and three controls (13%), and geographic



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relocation for five patients (6%) and two controls (9%). A smaller number of participants missed the baseline assessment but provided data at follow-up.

For the patients, stroke location was hemispheric in 82%, brainstem in 8% and cerebellar in 10%, and the NINDS classification was atheroembolic in 51%, cardioembolic in 19% and lacunar in 30%.

The study was approved by the ethics committees of the University of New South Wales and the Southeastern Sydney Illawara Area Health Service. All participants provided written informed consent.

Assessments

Baseline

Patients undertook functional tests and the Mini Mental State Examination (MMSE)²⁰ within 1 week of hospital admission, and a detailed medical and psychiatric examination (including a neuropsychological assessment) 3–6 months after the stroke or TIA. A subgroup also received a brain MRI scan at this time. Controls were assessed upon admission to the study.

Follow-up

The medical and psychiatric examination (including neuropsychological assessment), functional tests and MMSE were repeated at 12 months and 3 years after baseline. MRI scans were repeated at the 3-year follow-up only.

Medical, psychiatric and functional assessment

A medical and psychiatric history was obtained and questionnaires administered, including the Activities of Daily Living (ADL)²¹ and Instrumental ADL (IADL)²² scales, and the Social and Occupational Functioning Assessment Scale (SOFAS).²³ Informants completed the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE).²⁴ The occurrence of an interval stroke or TIA was indicated by history from patient and informant, and a review of the patient's hospital notes.

Neuropsychological assessment

The test battery addressed these cognitive domains: verbal memory, visual memory, working memory, attention, language, processing speed, visuoconstruction, praxis-gnosis, abstract reasoning, mental flexibility and verbal fluency (online supplementary table S1 shows the tests in each domain). Trained clinical psychologists performed the assessments, which took 2–3 h. Cognitive domain scores were derived by calculating z-scores for each test, using the control group's baseline mean and SD, and averaging across the tests in particular domains.²⁵ We calculated a composite neuropsychological test score by averaging the domain scores and transforming the results to z-scores.

MRI scans

MRI was performed using a 1.5 T Signa GE scanner (GE Systems, Milwaukee, USA) and the following protocol: 1.5 mm thick T1-weighted contiguous coronal sections through whole brain using a FSPGR sequence and 3D acquisition (TR 14.3 ms, TE 5.4 ms, FOV 25 cm, inplane resolution 0.977×0.977 mm²); and 4 mm thick (no gap between the slices) T2-weighted FLAIR coronal slices through whole brain (TR 8900 ms, TE 145 ms, TI 2200 ms, FOV 25 cm, matrix size 256×192). Scans were processed using Analyze (Mayo Foundation, Rochester Michigan, USA) and SPM99 (Cognitive Neuroscience Group, National Hospital for Nervous Diseases, London). Grey matter (GM),

WM and cerebrospinal fluid (CSF) volumes were obtained after segmentation of T1-weighted images. Total brain volume (TBV) was calculated as GM+WM, intracranial volume (ICV) as TBV+CSF and brain atrophy as (ICV-TBV)/ICV. Total WMH volume was determined from FLAIR sequences, with WMHs detected and delineated using a computer algorithm designed inhouse and implemented in Matlab. Hippocampal volumes were traced manually by trained operators. The hippocampus was traced until the slice anterior to a clear separation of the crus of the fornix from the wall of the lateral ventricle. The posterior segment of the hippocampus tail was traced from coronally-oriented images in an anterior-posterior direction until the facio-lar gyrus becomes the subsplenium gyrus curving around the postero-inferior margin of the splenium.

Homocysteine and genotyping

Total homocysteine levels were measured from fasting blood samples using Abbot IMX-automated, fluorescence-based enzyme immunoassays with a range of measurement 0.5–50 µmol/L and demonstrated high repeatability.²⁶ Genotyping for polymorphism on the apolipoprotein E gene (*APOE*) and the C677T mutation of the methylenetetrahydrofolate reductase enzyme gene (*MTHFR*) was carried out by PCR-based methods. Participants were classified as ε4 positive or negative for the *APOE4* polymorphism, and as T positive (TT, TC) or negative (CC) for the *MTHFR* C677T single nucleotide polymorphism (rs1801133).

Consensus diagnoses

Consensus diagnoses of dementia were made by a panel comprising a neuropsychiatrist, psychogeriatrician and neurologist, and one or more research psychologists. The criteria for dementia was two or more cognitive domains (not necessarily memory) with impairment (performance <5th centile on at least one test) and evidence of functional decline caused by the cognitive deficits (decline in SOFAS score of ≥20 from the pre-morbid estimate, or failure on one ADL item or two IADL items due to cognitive deficits).

Statistical analysis

Demographic and clinical characteristics of patients and controls were compared using t or χ^2 tests. Repeated-measures analyses of neuropsychological and MRI variables were conducted using linear mixed models. Unlike other repeated-measures approaches, linear mixed models are able to include participants missing data for some time-points.^{27 28} The models included group, time and group×time interaction terms. Neuropsychological analyses featured three groups: patients without an interval stroke/TIA, patients with an interval stroke/TIA and controls. With smaller numbers, MRI analyses featured only two groups, patients and controls. Adjustments for neuropsychological analyses were baseline age and education (both mean-centred) and sex, and for MRI analyses age, sex and time-varying ICV (mean-centred at both assessments). Missing values for education (seven cases) and age (one case) were replaced by zero (as these variables were mean-centred). We also used linear mixed models to investigate if certain baseline factors or an interval stroke/TIA predicted declines in composite neuropsychological test score and verbal memory in patients (adjusted for age, sex, education and ICV where appropriate). All linear mixed models had unstructured covariance matrices. Investigations were conducted to determine if and how the presence of any outliers affected our results (outlying values were identified for patients and controls separately as three or more SDs

Table 1 Demographic and baseline and 3-year follow-up clinical characteristics of patients and controls*

	Patients (n=183)†	Controls (n=97)†	p Value
Age (years)	71.91±9.07	71.07±6.07	0.36
Females	74 (40.4)	49 (50.5)	0.10
Education (years)	10.10±2.66	11.75±3.31	<0.001
Baseline clinical test scores			
MMSE	27.83±2.56	28.78±1.30	<0.001
ADL	5.26±1.35	5.97±0.18	<0.001
IADL	6.82±1.93	7.99±0.10	<0.001
IQCODE	3.10±0.25	3.08±0.16	0.46
Follow-up clinical test scores			
MMSE	27.60±3.04	29.19±0.90	<0.001
ADL	5.01±1.64	6.00±0.00	<0.001
IADL	6.28±2.31	7.89±0.42	<0.001
IQCODE	3.29±0.60	3.06±0.26	0.001
Coronary artery disease	55 (31.4)	13 (14.0)	0.002
Hypertension	107 (59.4)	33 (35.5)	<0.001
Diabetes	29 (16.2)	7 (7.6)	0.04
Atrial fibrillation	44 (24.9)	2 (2.2)	<0.001
Hypercholesterolaemia	68 (40.2)	21 (24.7)	0.01
Smoker (past or current)	108 (62.8)	40 (43.5)	0.004
Alcohol abuse	11 (6.1)	6 (6.7)	0.85

*Data are presented as either mean±SD or n (%).

†Maximum n, with percentages for participants with valid data.

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; IQCODE, Informant Questionnaire for Cognitive Decline in the Elderly; MMSE, Mini Mental State Examination.

above or below the mean). Analyses were conducted using IBM SPSS Statistics V20, and $p < 0.05$ considered statistically significant.

RESULTS

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of patients and controls, and the results of comparisons between these. The average age of all participants was 71.6 years (range 49–86), and 43.9% were women (this did not differ significantly between patients and controls). Controls averaged nearly 12 years of education, which was more than 1.5 years greater than patients. Controls had higher ADL (baseline 5.97 vs 5.26), IADL (baseline 7.99 vs 6.82) and MMSE (baseline 28.78 vs 27.83) scores than patients; they also had lower IQCODE scores at follow-up, but not at baseline (see table 1 for details). Compared with controls, the MMSE, ADL and IADL scores of patients decreased significantly from baseline to follow-up ($p = 0.012$, $p = 0.005$ and $p < 0.001$, respectively). Patients were also more likely than controls to have history of coronary artery

disease (31% vs 14%), hypertension (59% vs 36%), diabetes (16% vs 8%), atrial fibrillation (25% vs 2%) and hypercholesterolaemia (40% vs 25%), and to be past or current smokers (63% vs 44%). Patients missing follow-up data did not differ from patients with follow-up data on sex, education or baseline IQCODE, but were older (74.56 vs 70.05 years, $p = 0.001$) and had lower baseline ADL (4.79 vs 5.60, $p < 0.001$), IADL (5.92 vs 7.48, $p < 0.001$) and MMSE (27.11 vs 28.40, $p = 0.002$) scores. There were no significant differences in the rates of cardiovascular risk factors (see online supplementary table S2 for details), WMH volume or brain atrophy, but patients missing follow-up data had smaller amygdalae and hippocampi than patients with follow-up data (1.47 ± 0.28 mL vs 1.65 ± 0.30 mL, $p = 0.014$ and 5.28 ± 0.76 mL vs 5.61 ± 0.76 mL, $p = 0.056$, respectively).

Interval strokes and TIAs

In all, 42 patients (23.0%) had at least one stroke or TIA between baseline and follow-up, including 15 cases of TIA only, five of stroke only, 18 of both TIA and stroke, and four unknown. Patients with an interval stroke/TIA did not differ significantly from those without an interval stroke/TIA on age, education or *APOE4* status, but experienced greater declines in MMSE and composite neuropsychological test scores ($p = 0.021$ and $p < 0.001$, respectively).

Cognitive functioning

The numbers of participants with data available for the neuropsychological analyses are shown in table 2. Table 3 shows estimated mean values from the fitted linear mixed models for the controls and two patient groups (with and without an interval stroke/TIA). Across the cognitive domains investigated, scores were typically lower for patients than controls at both baseline and follow-up. For patients with an interval stroke/TIA, follow-up scores were frequently lower than baseline scores. The extent to which these differences are statistically significant is indicated by the parameter estimates also shown in table 3, and which are for the interactions between time and patient group (vs controls), separately for each group of patients. A negative parameter estimate indicates a greater decline in patients than controls, and a positive parameter estimate indicates a smaller decline in patients than controls. Patients with an interval stroke/TIA exhibited significantly greater decline in performance than controls on six of the 12 measures, whereas patients without an interval stroke/TIA declined more rapidly than controls only on verbal memory. For almost every cognitive domain, there were one or two participants for whom the difference between baseline and follow-up was an outlying value. Excluding these made no difference to the results, except for

Table 2 Numbers of participants contributing to the linear mixed models analyses of neuropsychological and MRI data

Assessment periods	Neuropsychological			MRI	
	Patients with interval stroke/TIA	Patients without interval stroke/TIA	Controls	All patients	Controls
Baseline only	64	17	22	49	13
Follow-up only	9	4	0	16	5
Baseline and follow-up	68	21	73	52	61
Total baseline	132	38	95	101	74
Total follow-up	77	25	73	68	66

TIA, transient ischaemic attack.

Table 3 Cognitive domain scores at baseline and follow-up in controls and patients either with or without an interval stroke/TIA and interactions (each patient group vs controls×time)*

Domain	Controls		Patients with interval stroke/TIA				Patients without interval stroke/TIA			
	Baseline	Follow-up	Baseline	Follow-up	Interaction		Baseline	Follow-up	Interaction	
					Parameter estimate	p Value			Parameter estimate	p Value
Attention	-0.11±0.13	-0.19±0.14	-0.51±0.19	-1.19±0.23	-0.60±0.25	0.01	-0.83±0.11	-0.73±0.13	0.17±0.17	0.32
Verbal memory	-0.10±0.10	0.16±0.13	-0.08±0.16	-0.27±0.21	-0.44±0.21	0.03	-0.12±0.09	-0.41±0.12	-0.54±0.14	<0.001
Visual memory	-0.07±0.11	0.31±0.12	-1.00±0.17	-1.04±0.20	-0.41±0.21	0.06	-0.86±0.10	-0.48±0.12	0.00±0.15	0.98
Processing speed	-0.10±0.16	-0.02±0.17	-1.05±0.25	-1.70±0.29	-0.72±0.23	0.002	-1.09±0.15	-1.14±0.17	-0.12±0.16	0.44
Reasoning	-0.11±0.12	0.06±0.13	-0.99±0.19	-0.86±0.21	-0.04±0.22	0.84	-1.11±0.11	-0.73±0.12	0.21±0.15	0.16
Working memory	-0.10±0.10	-0.17±0.11	-0.61±0.15	-1.01±0.18	-0.33±0.16	0.03	-0.66±0.09	-0.69±0.10	0.04±0.11	0.70
Language	-0.01±0.15	0.16±0.17	-0.33±0.22	-1.33±0.28	-1.16±0.27	<0.001	-0.82±0.13	-0.83±0.16	-0.17±0.18	0.36
Praxis-gnosis	-0.08±0.18	0.03±0.14	-0.92±0.28	-0.57±0.24	0.23±0.36	0.53	-0.92±0.16	-0.47±0.14	0.32±0.25	0.20
Visuoconstruction	-0.11±0.13	-0.14±0.14	-1.16±0.21	-1.50±0.24	-0.30±0.22	0.18	-0.76±0.11	-0.87±0.13	-0.6±0.15	0.66
Mental flexibility	-0.10±0.27	-0.19±0.22	-1.27±0.45	-2.14±0.42	-0.78±0.50	0.11	-2.14±0.25	-1.64±0.23	0.59±0.32	0.06
Verbal fluency	-0.10±0.10	-0.11±0.12	-0.85±0.15	-1.16±0.20	-0.29±0.20	0.14	-0.89±0.09	-0.85±0.12	0.04±0.14	0.74
Composite score	-0.10±0.09	-0.03±0.10	-0.75±0.14	-1.22±0.15	-0.54±0.10	<0.001	-0.96±0.08	-0.84±0.08	0.04±0.07	0.56

*Mean scores (±SE) are estimated mean values, adjusted for age, sex and education. Parameter estimates (±SE) are for the interaction terms (patient group vs controls×time) of the linear mixed models. A negative parameter estimate indicates a greater decline in patients than controls, and a positive parameter estimate indicates a smaller decline in patients than controls. p Values are for the statistical significance of the interaction parameter estimates. Analyses were repeated with outliers excluded: a significant decline in verbal fluency for patients with an interval stroke/TIA (p=0.016) was the only difference to the presented results. TIA, transient ischaemic attack.

the additional finding of a significant decline in verbal fluency for patients with an interval stroke/TIA.

MRI

The numbers of participants with data available for the MRI analyses are shown in table 2. The estimated mean values (figure 1) and parameter estimates (table 4) of fitted models indicate significantly greater WMH volumes in patients (baseline 37 mL; follow-up 42 mL) than controls (baseline 16 mL; follow-up 21 mL). Hippocampus and amygdala volumes decreased significantly and WMH volume and brain atrophy increased significantly over time across all participants. The increase in brain

atrophy of around 0.1 across all participants was significantly (though only slightly) greater in patients than controls.

Incident dementia

The rate of incident dementia between baseline and follow-up was significantly higher in patients (20 from 113, 17.7%) than controls (one from 85, 1.2%; $\chi^2=13.97$, p<0.001). This analysis of incident dementia rates excluded 32 patients with dementia at baseline and participants lost to the 3-year follow-up not diagnosed with dementia at 12 months (18 controls, 59 patients). To see if these exclusions could have influenced our results, we conducted sensitivity analyses with all

Figure 1 Change in brain atrophy and hippocampus, amygdala and total white matter hyperintensity (WMH) volumes between baseline and follow-up in stroke patients (black circles) and controls (open circles). Points represent the estimated mean values (±SE) for the group (patients, controls)×time (baseline, follow-up) interaction term of linear mixed models. Atrophy was calculated as the ratio of cerebrospinal fluid (CSF) to intracranial volume (ICV).

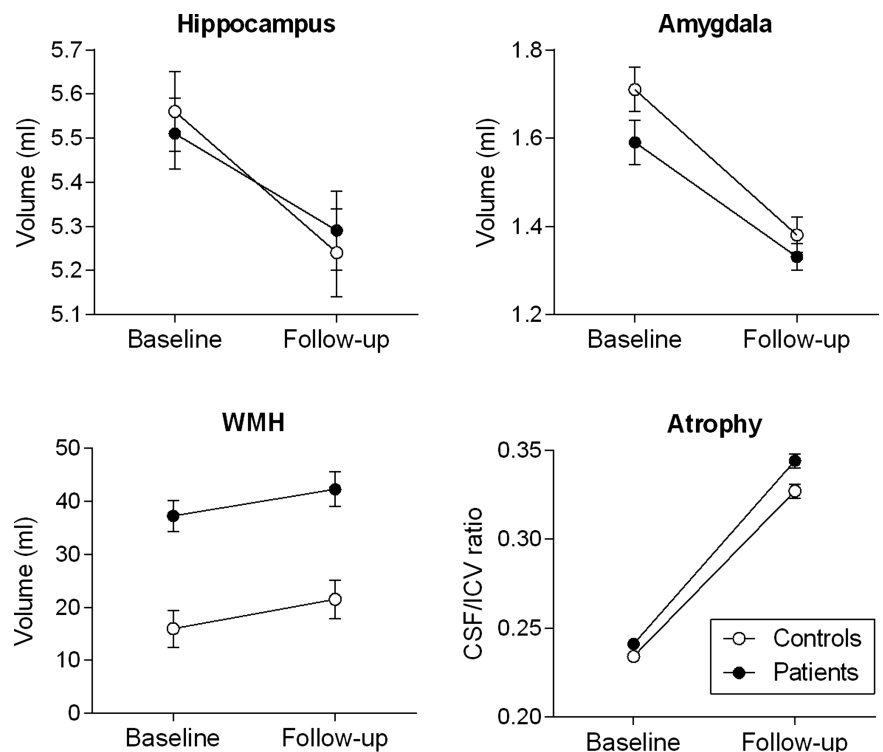


Table 4 Linear mixed model parameter estimates (\pm SE) for MRI variables

MRI variable	Patients vs controls		Follow-up vs baseline		Change over time, patients vs controls	
	Estimate	p Value	Estimate	p Value	Estimate	p Value
Hippocampus*	-0.04 \pm 0.11	0.67	-0.31 \pm 0.11	0.007	0.09 \pm 0.15	0.55
Amygdala*	-0.12 \pm 0.06	0.06	-0.33 \pm 0.05	<0.001	0.07 \pm 0.08	0.34
WMHs*	0.02 \pm 0.00	<0.001	0.00 \pm 0.00	<0.001	0.00 \pm 0.00	0.71
Atrophy†	0.00 \pm 0.00	0.10	0.09 \pm 0.00	<0.001	0.10 \pm 0.00	0.04

*Estimates calculated using volume in mL and adjusted for age, sex and time-varying intracranial volume.

†Estimates adjusted for age and sex.

WMHs, white matter hyperintensities.

missing participants classified as either developing or not developing incident dementia. The results were unchanged in these sensitivity analyses, with patients continuing to show a higher rate of incident dementia than controls ($p \leq 0.001$).

Predictors of cognitive decline in stroke patients

Investigations of whether certain baseline factors predicted declines in composite neuropsychological test score and verbal memory were performed for all stroke patients, and repeated for those without an interval stroke/TIA. Table 5 shows parameter estimates from the fitted linear mixed models for the interactions between predictor and time (follow-up vs baseline), adjusted for age, sex and education. A negative parameter estimate indicates greater decline and a positive parameter estimate indicates less decline if meeting a categorical factor (eg, female vs male) or for increasing values of a continuous factor (eg, hippocampus volume). Across all patients, there were greater declines in

composite score for women and individuals with smaller hippocampi. Patients without an interval stroke/TIA showed greater declines in composite score if *APOE* $\epsilon 4$ positive. The same baseline factors had some associations with verbal memory decline. Across all patients, women declined more than men (estimate: -0.51, SE=0.19, $p=0.011$). Higher WMH volume was also associated with greater verbal memory decline when an additional four patients with high WMH volumes (>3 SD above the mean) were included (estimate: -7.28, SE=3.14, $p=0.024$; otherwise estimate: -2.82, SE=4.94, $p=0.571$). Patients without an interval stroke/TIA showed significantly greater verbal memory decline if *APOE* $\epsilon 4$ positive (estimate: -0.95, SE=0.35, $p=0.011$), and tended to show greater decline if having smaller hippocampi (estimate: 0.522, SE=0.26, $p=0.055$). An interval stroke/TIA was associated with greater decline in composite score (estimate: -0.58, SE=0.12, $p<0.001$), but not in verbal memory (estimate: 0.10, SE=0.23, $p=0.647$).

Table 5 Linear mixed model parameter estimates (\pm SE) for baseline predictors of decline in composite neuropsychological test scores in stroke/TIA patients*

Predictor	All patients		No interval stroke/TIA	
	Parameter estimate	p Value	Parameter estimate	p Value
Demographic/clinical				
Age in years	0.00 \pm 0.00	0.82	0.00 \pm 0.00	0.67
Female	-0.31 \pm 0.11	0.01	-0.22 \pm 0.10	0.04
Education in years	0.02 \pm 0.02	0.20	0.01 \pm 0.01	0.59
MMSE score	-0.02 \pm 0.03	0.48	-0.04 \pm 0.03	0.20
IQCODE score	-0.43 \pm 0.30	0.15	0.14 \pm 0.28	0.61
Cardiovascular risks				
Hypertension	-0.16 \pm 0.12	0.20	-0.12 \pm 0.11	0.25
Diabetes	0.01 \pm 0.16	0.90	0.04 \pm 0.15	0.80
High cholesterol	0.16 \pm 0.12	0.18	-0.06 \pm 0.10	0.56
Smoker	0.21 \pm 0.12	0.09	0.17 \pm 0.11	0.12
Laboratory measures				
Homocysteine in μ mol/L	0.00 \pm 0.00	0.89	0.00 \pm 0.00	0.85
<i>APOE</i> $\epsilon 4$ positive	0.19 \pm 0.21	0.36	-0.48 \pm 0.17	0.009
<i>MTHFR</i> T positive	-0.12 \pm 0.20	0.53	0.14 \pm 0.18	0.43
MRI				
Atrophy	-0.33 \pm 2.79	0.90	-1.51 \pm 2.15	0.48
Hippocampus in mL†	0.36 \pm 0.13	0.01	0.30 \pm 0.11	0.008
WMHs in L†	-0.93 \pm 2.55	0.71	-1.05 \pm 2.44	0.66

*Parameter estimates are for predictor \times time (follow-up vs baseline) interaction terms adjusted for age, sex and education. A negative parameter estimate indicates greater decline and a positive parameter estimate indicates less decline if meeting a categorical factor (eg, female vs male) or for increasing values of a continuous factor (eg, hippocampus volume).

†Additionally adjusted for intracranial volume and one outlier (volume <3 SD) excluded.

‡Additionally adjusted for intracranial volume and four outliers (volume >3 SD) excluded.

APOE4, apolipoprotein E; IQCODE, Informant Questionnaire for Cognitive Decline in the Elderly; MMSE, Mini Mental State Examination; *MTHFR*, methylenetetrahydrofolate reductase C677T single nucleotide polymorphism; TIA, transient ischaemic attack; WMHs, white matter hyperintensities.

DISCUSSION

This study reports the progression of cognitive impairment in stroke/TIA patients enrolled in the Sydney Stroke Study over 3 years. Patients did not typically decline more than controls in most cognitive domains, but they started from a lower baseline. The exception was that patients showed greater verbal memory decline (-0.45 SD) than controls. This difference was large and highly significant, but in being for only one cognitive domain contrasts with the far more pervasive decline observed in the 23% of patients with an interval stroke/TIA. These patients showed significantly greater declines in MMSE and composite cognitive scores, as well as on scores for verbal, visual and working memory, language, attention, and processing speed. These findings expand upon our 1-year follow-up report for this cohort,¹⁹ when patients similarly showed greater declines in MMSE, composite and verbal memory scores than controls. Patients also showed greater decline than controls in visuoconstruction over 1 year, but not over 3 years. Patients with a subsequent stroke showed accelerated decline in global cognitive functioning over both follow-up intervals. However, our 3-year findings identify a number of individual cognitive domains in which patients with a subsequent stroke show accelerated decline.

The rates of dementia present a somewhat different picture, with 17.7% of patients diagnosed with dementia in this period; an annual incidence of 5.9%. Only 1.2% of controls received this diagnosis. The apparent discrepancy between the somewhat similar rates of decline in cognitive domain scores and the higher dementia incidence in patients may be explained by patients having lower baseline cognitive performance.

It is important however to consider participant attrition, especially for patients. The majority of attrition was due to death or ill-health, and those not completing the 3-year follow-up were 5 years older and had lower baseline MMSE scores (-2.9 points). This indicates selective attrition of the more cognitively impaired, and an outcome that is likely to be positively biased. The use of linear mixed models attempted to take this into consideration, and sensitivity analyses showed that dementia rates were higher in patients.

Previous reports have provided varying rates of cognitive decline in stroke patients, with annual declines in MMSE of -1.1 ,⁵ -1.77 ,¹⁵ -0.82 ¹⁶ and -0.78 ¹⁸ points reported by different studies. Other studies have also reported low rates of incident dementia in stroke patients.^{9 29-31} Our study supports this, and also suggests that, as expected, those with another stroke/TIA show greater decline. An interval stroke/TIA accelerated cognitive change by -1.62 (vs -0.08) points in our patients, consistent with previous reports.^{5 30 31} The concept of multi-infarct dementia that this finding supports must however be elaborated, as another predictor of decline in those with an interval stroke/TIA was WM lesions, when their level was high. The cognitive impairment, and thereby dementia, is therefore the combined effect of both large and small vessel disease, with the former making a bigger contribution, and an interval stroke/TIA having a more discernible effect is not surprising. A recent review concluded that a stroke doubled the risk of dementia incidence in individuals >65 -years-old, but had no effect in individuals >85 -years-old.²⁹ The rate of decline, with or without an interval stroke/TIA, was however less than that seen in early AD.³² Interventions trials in VaD must also take this into consideration when planning the sample size and duration of intervention.

The greater decline in verbal memory we observed is worthy of comment. We have previously argued that frontal-executive dysfunction is an early feature of vascular cognitive disorders,

while early decline in memory favours AD.² Deducing the neuropathological substrate of the memory decline is however difficult, given the logical memory subtest of the WMS-R addresses complex processes involving registration, retention and recall of structured information, any of which may be affected by WM lesions or front-subcortical system disturbances without the hippocampus being directly affected.³³ The memory decline may therefore occur from vascular or Alzheimer-type pathology, and the cognitive profile does not permit discernment between these.

We examined neuroimaging and genetic factors to investigate the pathological basis of cognitive decline. Patients and controls both showed reductions in whole brain, hippocampal and amygdala volumes and increases in WMH volumes, but whole brain atrophy was greater in patients. We also found that smaller baseline hippocampi predicted greater memory decline. However, the attrition of participants with smaller hippocampi and amygdalae at baseline suggests that associations between these structures and cognitive decline may have been underestimated. Verbal memory decline in patients without an interval stroke/TIA was also associated with having an APOE $\epsilon 4$ allele, which is strongly associated with Alzheimer-type pathology but only inconsistently with vascular cognitive disorders.³⁴ Previous studies have shown that stroke affects dementia incidence in APOE $\epsilon 4$ negative individuals only.^{35 36} Our finding relating APOE $\epsilon 4$ to cognitive decline in the absence of stroke is consistent with this. We infer that the cognitive decline in our stroke patients is probably due to a combination of vascular and neurodegenerative processes, with the former predominating in those with repeat vascular events.

Consistent with previous reports,²⁹ decline was not explained by baseline cognitive function, prestroke cognitive decline or education. Cerebrovascular risk factors also did not emerge as significant predictors of cognitive change. While hypertension, diabetes, hypoxic/ischaemic and other cerebrovascular risk factors contribute to vascular cognitive disorders, they are usually not identified as predicting decline.^{5-7 9 10} Some possible explanations for this include: (i) the risk factors do not contribute beyond accounting for the stroke and WMH risk at baseline; (ii) the contribution is accounted for by their impact on baseline cognitive status; or (iii) the small magnitude of decline limits the statistical power to detect risk factors.

Our study is characterised by detailed and careful assessments but has some limitations. First, many potential participants were excluded for being unable to complete assessments, biasing our sample toward the less severely affected. Second, attrition, due mainly to illness or death, biased our sample toward the healthy end of the spectrum. This is inevitable in stroke patients, but we attempted to overcome this limitation by using linear mixed models and performing a sensitivity analysis. Nevertheless, it is possible that the true magnitude of associations between predictors and cognitive decline was attenuated in our study by survivor bias. Third, controls had more years of education than patients, but this was controlled for statistically. Fourth, our study probably underestimated the extent of vascular pathology as aspects of cerebrovascular disease such as silent lacunar infarct and microbleeds were not examined. Fifth, the use of self-report measures in participants with memory problems could be considered a challenge to the validity of some results. Sixth, a follow-up of 3 years may have been insufficient time for vascular risk factors or stroke/TIA to exert the full effects.

In conclusion, our study supports a picture of slow cognitive decline in stroke/TIA patients who do not experience a further

stroke or TIA. In contrast, patients reporting further strokes or TIAs during follow-up exhibited significant and much greater cognitive decline. This was evident for general cognitive functioning and many cognitive domains, with possible contributions from both vascular and neurodegenerative processes.

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Competing interests PSS, DML, JDC and WW report no competing interests. HB is an investigator for Pfizer, Novartis, Janssen, Lundbeck and Lilly, a sponsored speaker for Pfizer, Novartis, Janssen and Nutricia, and is on the advisory boards of Pfizer, Novartis, Janssen, Lundbeck and Nutricia.

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Supplementary table 1 Tests assigned to cognitive domains

Domain	Tests
Verbal memory	Logical Memory I and II subtests (WMS-R) ¹
Visual memory	Visual Reproduction I & II (WMS-R) ¹
Working memory	Digit Span backwards, Arithmetic (WAIS-R) ²
Attention	Digit Span forwards (WAIS-R) ² Mental Control (WMS-R) ¹
Language	15 item Boston Naming Test ³
Processing speed	Trail Making Test Part A ⁴ Symbol Digit Modalities Test ⁵
Visuoconstruction	Block Design (WAIS-R) ² Copying simple figures
Praxis-gnosis	Ideomotor apraxia subtest items (WAB) ⁶ Finger gnosis and stereognosis ^{7,8}
Abstract reasoning	Similarities, Picture Completion (WAIS-R) ²
Mental flexibility	Colour Form Sorting Text ⁹ Trail Making Test Part B ¹⁰
Verbal fluency	Phonemic (FAS) and semantic (animals) ¹¹

WAB, Western Aphasia Battery; WAIS-R, Wechsler Adult Intelligence Scale - Revised; WMS-R, Wechsler Memory Scale – Revised.

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Supplementary Table 2 Vascular risk factors in patients either with or without an interval stroke/TIA

Risk factor	Interval stroke/TIA (n = 42)*	No interval stroke/TIA (n = 141)*	p value
Coronary artery disease	16 (40.0)	39 (28.9)	0.184
Hypertension	23 (54.8)	84 (60.9)	0.480
Diabetes	9 (22.0)	20 (14.5)	0.255
Atrial fibrillation	12 (28.6)	32 (23.7)	0.524
Hypercholesterolemia	13 (31.7)	55 (43.0)	0.201
Smoker (past or current)	27 (64.3)	80 (61.5)	0.750

Values are n (%)

*Maximum n, with percentages for participants with valid data.

TIA, transient ischemic attack.