Stroke

ORIGINAL CONTRIBUTION

Dynamic Regional Brain Atrophy Rates in the First Year After Ischemic Stroke

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BACKGROUND AND PURPOSE: Brain atrophy can be regarded as an end-organ effect of cumulative cardiovascular risk factors. Accelerated brain atrophy is described following ischemic stroke, but it is not known whether atrophy rates vary over the poststroke period. Examining rates of brain atrophy allows the identification of potential therapeutic windows for interventions to prevent poststroke brain atrophy.

METHODS: We charted total and regional brain volume and cortical thickness trajectories, comparing atrophy rates over 2 time periods in the first year after ischemic stroke: within 3 months (early period) and between 3 and 12 months (later period). Patients with first-ever or recurrent ischemic stroke were recruited from 3 Melbourne hospitals at 1 of 2 poststroke time points: within 6 weeks (baseline) or 3 months. Whole-brain 3T magnetic resonance imaging was performed at 3 time points: baseline, 3 months, and 12 months. Eighty-six stroke participants completed testing at baseline; 125 at 3 months (76 baseline follow-up plus 49 delayed recruitment); and 113 participants at 12 months. Their data were compared with 40 healthy control participants with identical testing. We examined 5 brain measures: hippocampal volume, thalamic volume, total brain and hemispheric brain volume, and cortical thickness. We tested whether brain atrophy rates differed between time points and groups. A linear mixed-effect model was used to compare brain structural changes, including age, sex, years of education, a composite cerebrovascular risk factor score, and total intracranial volume as covariates.

RESULTS: Atrophy rates were greater in stroke than control participants. Ipsilesional hemispheric, hippocampal, and thalamic atrophy rates were 2 to 4 times greater in the early versus later period.

CONCLUSIONS: Regional atrophy rates vary over the first year after stroke. Rapid brain volume loss in the first 3 months after stroke may represent a potential window for intervention.

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Key Words: atrophy ■ hippocampus ■ magnetic resonance imaging ■ risk factors ■ thalamus

Brain atrophy is a hallmark of neurodegenerative disease. Imaging signatures of Alzheimer disease (AD) are well described. It is known that brain atrophy precedes and predicts dementia in longitudinal studies of people at risk for AD, and predates any cognitive change detectable on current screening instruments by several years.[1,2] Increasing our understanding of brain volume trajectories to detect people at risk of cognitive decline—and develop interventions to prevent this decline—is of great importance. Yet longitudinal brain volume changes in patients with stroke or at risk of vascular dementia are scarcely reported.[3,4]

Hippocampal atrophy[5] is both a manifestation of vascular risk factors and a core feature of vascular cognitive impairment.[6,7] All cerebrovascular risk factors are associated with brain volume loss and increased risk of dementia,[8,9] including midlife and untreated hypertension,[10] type 2 diabetes mellitus,[11] high midlife body mass index,[12]

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Nonstandard Abbreviations and Acronyms

AD	Alzheimer disease
APOE ε4	apolipoprotein epsilon-4 allele
CANVAS	Cognition and Neocortical Volume After Stroke
CONSORT	Consolidated Standards of Reporting Trials
MRI	magnetic resonance imaging
TBV	total brain volume

smoking,[9] atrial fibrillation,[13] and apolipoprotein epsilon-4 allele (*APOE* ε4) status.[14] Structural brain aging occurs at an accelerated rate in people with cerebrovascular risk factors, manifesting as interval strokes, white matter hyperintensities of presumed vascular origin,[15] and neurodegeneration.[16,17]

It is not understood whether rates of brain atrophy are steady before or following a stroke, or whether there are periods of more rapid brain volume loss in regions remote to the infarct. Patients with stroke have often been imaged at varying periods after stroke, making it difficult to disentangle the effect of the acute stroke itself. This has left a gap in our understanding for potential windows of intervention to prevent poststroke brain atrophy and associated cognitive decline.

One way of interrogating the effect of the acute stroke lesion on brain atrophy trajectories is to examine the rates of atrophy over 2 or more proceeding time periods. We sought to examine the trajectories of regional brain volume changes in the first year following stroke. The CANVAS study (Cognition and Neocortical Volume After Stroke) is a longitudinal study in people following ischemic stroke, comparing brain volume and cognitive function over 3 years with a group of healthy age- and sex-matched control participants.[18] Here, we present imaging data only from the first year of follow-up of CANVAS, as 12 months presents a pragmatic and practical time period for clinical trials but is usually too early to detect cognitive decline. We selected 5 brain measures: hippocampal, thalamic, total brain and hemispheric brain volumes, and cortical thickness. These measures were chosen based on previously published studies of regions that were shown to be affected by stroke and vascular risk factors. We analyzed data as ipsilesional or contralesional to the stroke. As well as total brain volume (TBV)—the usual metric used in these analyses—we have included hemispheric brain volumes, to better capture the effect of the stroke lesion. We compared values at each time point with control participants and examined rates of atrophy within these regions over the year, testing for differences in atrophy rates between the 2 time periods.

MATERIALS AND METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Experimental Design

Details of the CANVAS study protocol including primary outcome measures and sample size calculation can be found in our published protocol article.[18] Here, we use a sample of all participants with available scans at each of the 3 time points to examine brain volume trajectories over the first year after stroke.

Inclusion and Exclusion Criteria

All stroke subtypes were included, as brain atrophy and subsequent cognitive decline have been reported in any stroke subtype, regardless of cause or site.[19] Although we note that brain stem strokes are least strongly associated with poststroke cognitive impairment and dementia, this group often have small vessel disease and were included for completeness. Patients were recruited for study entry at 2 time points: within 6 weeks of stroke (baseline) and 3 months. This allowed for inclusion of people unable to participate at an earlier time point, such as those with severe stroke or aphasia, and the resolution of any subacute stroke-associated illness. Participants were excluded if they had a preexisting history of significant cognitive decline (based on participant and informant history), could not undergo 3T magnetic resonance imaging (MRI), or if intercurrent illness—including psychiatric illness or delirium—precluded cognitive assessment. Patients with transient ischemic attacks or no confirmed diffusion-weighted imaging change on MRI were not included.

We obtained information about age, years of education, handedness, marital status, stroke and dementia family history, and alcohol consumption (low [≤14 standard drinks per week] or high [>14 standard drinks per week]) via interview. Depression, hypertension, type II diabetes mellitus, hypercholesterolemia, and atrial fibrillation were defined via a physician diagnosis and participant report and via the use of medications for these conditions at the time of stroke or inclusion in the study. Smoking pack-years was defined as the number of cigarette packs smoked per day multiplied by the number of years the participant smoked. Body mass index was calculated using weight and height measurements obtained on the day of the assessment, divided into low (<25) and high (≥25) groups.

Stroke Participants

Patients with first-ever or recurrent ischemic stroke were recruited from the Stroke Units at 3 Melbourne hospitals (Austin, Royal Melbourne, and Box Hill) between April 2012 and July 2015. The study was approved by each of the hospital human research ethics committees.[18] Patients provided consent in accordance with the Declaration of Helsinki. Strokes were classified with respect to site, side, and cause.[20] The presence of ischemic stroke was a clinical diagnosis, confirmed radiologically on clinical computed tomography or MRI for the incident event. A total of 135 patients with stroke and 40 control participants were recruited to the study—see Figure 1 for CONSORT (Consolidated Standards of Reporting Trials) diagram. Strokes

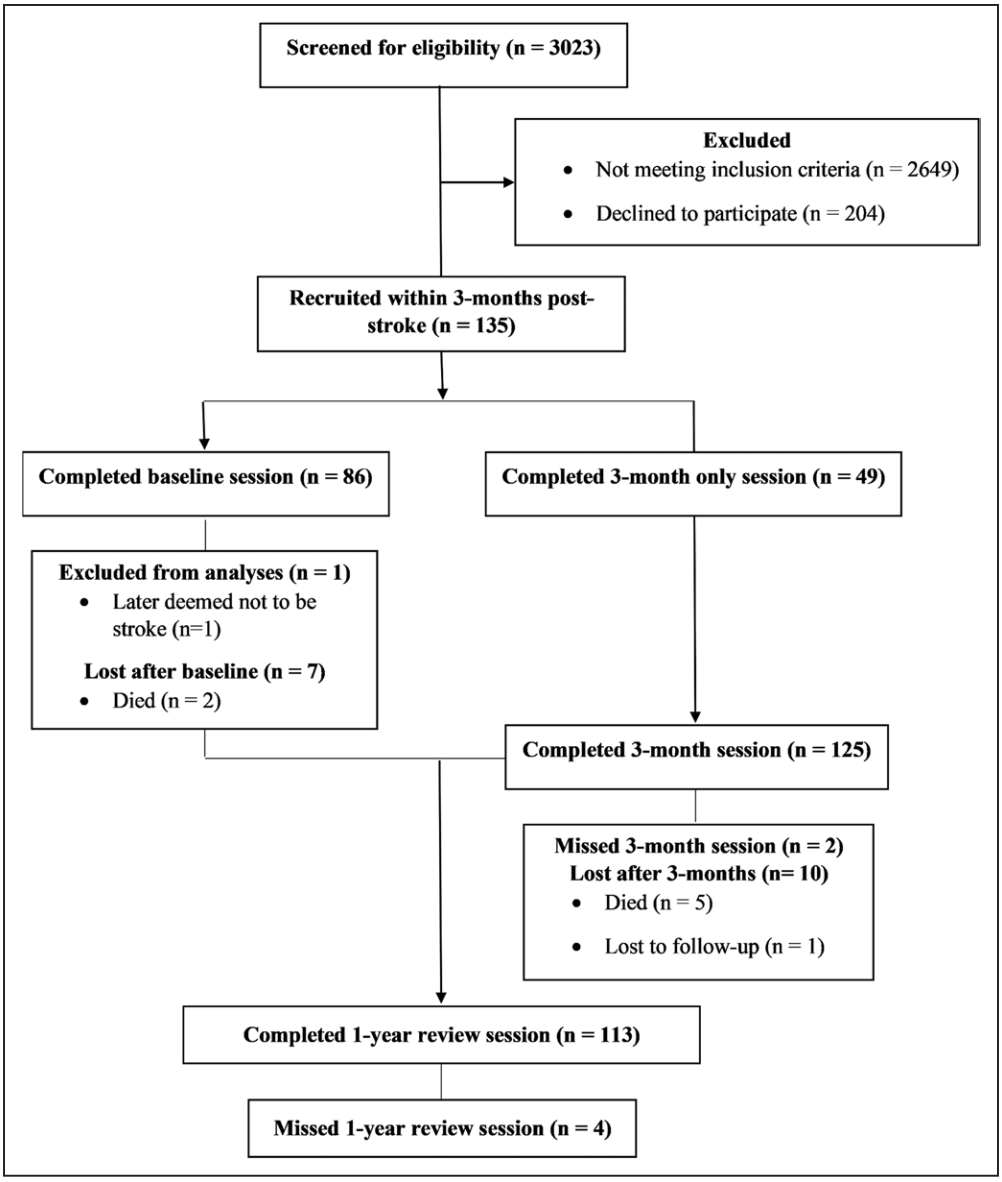

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) figure.
CONSORT figure representing stroke participants screened and included over the study recruitment period.

were in all vascular territories (Figure I in the Data Supplement). The mean number of days from symptom onset to MRI scan for baseline imaging for stroke participants was 25.5±9.2 days. No participant was scanned within the first 2 weeks of their stroke to allow edema to resolve. Eighty-six stroke participants were assessed at baseline, with 76 available for follow-up at 3 months. One participant was later excluded because MRI did not confirm diffusion-weighted imaging changes of ischemic stroke. A further 49 people were recruited at the delayed recruitment time point, but one was unable to complete MRI scanning. Nine participants withdrew from the study or were unable to attend the 3-month session, and a further 22 stroke participants did not attend the 12-month session, meaning a total of 125 stroke participants completed the 3-month session and 113 participants completed the 12-month session. See Table I in the Data Supplement for details of missing participant demographic and stroke characteristics.

The Short Form Informant Questionnaire on Cognitive Decline in the Elderly, validated in stroke,[21] was used on recruitment to detect the presence of undiagnosed pre-stroke cognitive decline. The authors screened participants for preexisting cognitive decline through discussions with participants, their next-of-kin, their general practitioner, and hospital staff. Longitudinal cognitive testing is done for the CANVAS study, but these data do not form part of the presented analyses here.[18]

Control Participants

Control participants without a history of transient ischemic attack or stroke were recruited from volunteers and a pool of people previously identified as interested in imaging studies. Control participant testing was identical to patient testing. Participant inclusion and exclusion criteria were the same as for the stroke patients except for the presence of stroke. Forty

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control participants completed sessions at each time point, but we excluded data for one participant at the 12-month time point because they suffered a silent stroke between 3 and 12 months (detected on research MRI scan).

Blinding

By the nature of the longitudinal study design, we were blinded to the outcome of interest. Furthermore, participants were assigned a unique identifier at recruitment. Stroke lesions were identified via inspection of images for tracing. However, all other estimates of volumes and cortical thickness were performed using automated methods designed for longitudinal analysis and performed on all participants in an identical way.

Image Acquisition and Processing

Whole-brain images were acquired on a 3T Siemens Tim Trio Scanner with a 12-channel head coil (Siemens, Erlangen, Germany). The MR images for the presented analyses were acquired using a T1-weighted 3-dimensional magnetization-prepared rapid gradient sequence with the following parameters: 160 coronal slices, repetition time RT=1900 ms, echo time TE=2.6 ms, inversion time TI=900 ms, flip angle=9°, matrix size=256×256, slice thickness=1 mm, and voxel size=1×1×1 mm^3 isotropic. High-resolution, 3-dimensional sampling perfection with application-optimized contrasts using different flip angle evolutions fluid-attenuated inversion recovery images were also acquired for white matter hyperintensity estimation and stroke lesion tracing: 160 sagittal slices, 1 mm thick, RT=6000 ms, TE=380 ms, 120° flip angle, and 256×256 acquisition matrix.

Cortical reconstruction and volumetric segmentation were performed with the longitudinal stream in FreeSurfer (version 6.0)[22] (http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing), recognized for its high level of precision and accuracy for detection of brain volume change. We have assessed FreeSurfer's hippocampal segmentation capability compared with manual tracing, recording a Shrout's intraclass correlation coefficient of 0.85 for FreeSurfer v5.3 and 0.87 for FreeSurfer v6.022.[23] Stroke lesions were traced for stroke volume estimation and for allocation of ipsilesional or contralesional status but were not masked. For control participants, we used an average between left and right volumes for comparison.

Statistical Analysis

Statistical analyses were performed in MATLAB (Statistics Toolbox, Release 2018a, The MathWorks, Inc, Natick, MA). All analyses were 2-tailed and used an α-level of 0.05 to determine statistical significance. Differences between groups on demographic and clinical variables at each time point and between participants with missing data and those included in the study were examined using independent samples *t* tests (continuous variables, parametrically distributed scores), Mann-Whitney *U* tests (continuous variables, nonparametrically distributed scores), and Fisher exact tests (2×2 categorical variables) as appropriate.

We used a linear mixed-effect multivariable regression model, where estimated volumes and cortical thickness were taken as the dependent variables. The model used a maximal effect structure with uncorrelated random intercept and random slope in addition to group, time, and group-time interaction as fixed effects and included the following covariates: age, sex, years of education, a composite cerebrovascular risk factor score, and total intracranial volume. The latter were checked for collinearity, and the model residuals were checked for normality and heteroscedasticity. Age was included to correct for loss of brain volume due to normal aging; sex to account for sexual dimorphism; education to adjust for its protective effect on cerebral structures; and total intracranial volume to control for head size variations (see Data Supplement for details). Cerebrovascular risk factor was included for their known association with brain atrophy. We calculated this as the sum of known risk factors, including obesity (body mass index ≥30 kg/m^2), hypertension, cholesterol, type II diabetes mellitus, ischemic heart disease, atrial fibrillation, smoking (≥1 cigarette/day), and alcohol consumption (≥14 units/wk). The risk scores were equally weighted and a sum ≥2 indicated a risk in the composite cerebrovascular risk factor array.

Hereafter, we refer to relative reduction in thickness or volume over a time period as percent atrophy and to absolute reduction per unit time as rate of atrophy (expressed in mm or mm^3/d). Rates of atrophy were computed within-group for early and later periods. For this study, we termed the change in volume between the baseline and 3-month scan as the early period and that between 3 and 12 months as the later period. Finally, we termed the period between baseline and 12-month time points as full period rather than annualized, as the interval was closer to 10 months. Family wise error due to multiple comparisons across regions of interest was controlled for using a 5% false discovery rate.[24]

All participants with evaluable scans were included. We performed a separate analysis including only participants with known APOE status (Table II in the Data Supplement) to test whether the inclusion of the 14 participants without known APOE status could have contributed bias if, say by chance, they were all APOE ε4 (apolipoprotein epsilon-4 allele) heterozygotes. AQ7

RESULTS

Group Demographics

A CONSORT figure has been included to summarize recruitment (Figure 1). There were no significant differences in age, sex, *APOE* ε4 status, and cognitive change scores between stroke patients and controls at each time point (Table III in the Data Supplement). Informant Questionnaire on Cognitive Decline in the Elderly scores for stroke and control participants were comparable at baseline. However, stroke participants had less years of education and had lower estimated full-scale IQ scores as estimated by the National Adult Reading Test.

Stroke characteristics at each time point are included in Table IV in the Data Supplement. Lesion location was very heterogeneous (Figure I in the Data Supplement). None of the acute stroke lesions were found in the hippocampi. One participant had a prior chronic stroke

affecting their hippocampus so was excluded from the hippocampal volume estimates.

Significance of Covariates

Age was significantly associated with all region of interests, as was total intracranial volume except for cortical thickness. Sex was associated with cortical thickness, and cerebrovascular risk factor score was only associated with TBV. Number of years of education was significantly associated with both ipsilesional and contralesional hippocampal volumes.

Percent and Rates of Atrophy Between Groups

A forest plot of within-group amount of atrophy over each time period is shown in Figure 2, mean percent amounts for volumes and thicknesses are shown in Figures 3 and 4, and daily rates of atrophy are shown in Figure 5. CIs and significance values are summarized in Table V in the Data Supplement, with a list of differences between groups (control as reference) in Table VI in the Data Supplement.

Control Group

Percent atrophy was comparable for all region of interests except for TBV over the full period (P=0.04). Over the full period, there was an average 0.38% reduction in cortical thickness, 0.81% reduction in hippocampal volume, 0.71% reduction in thalamic volume, and 0.42% reduction in TBV (Figure 3, Table V in the Data Supplement). There was no difference in atrophy rates or brain volumes between the right and left hemispheres. There was no difference in cortical thickness change between the early and later periods; that is, brain volume and thickness loss were comparable across the time periods.

Stroke Group

TBV Change

Compared with controls, TBV was significantly lower at 12 months, but not at other time points (Figures 2 and 3, Table V in the Data Supplement). Percent atrophy in the stroke group was significantly greater than controls over the early (0.58%) and later (0.54%) time periods with a rate of atrophy (≈824 mm^3/d) nearly 4 times higher in the early compared with later period (P<0.001, Figure 5). We found no correlation with TBV and stroke lesion volume.

Hemispheric Brain Volume Change

Percent atrophy was significantly greater than controls over the early and later time periods for both the ipsilesional (−0.84% to −0.78%) and contralesional (−0.27% to −0.31%) hemispheres (Figures 2 and 3). However, brain volume loss was greater ipsilesionally than contralesionally and was most rapid in the early period (−60.3 mm^3/d ipsilesionally cf. −19.2 mm^3/d contralesionally). It remained twice that of the contralesional hemisphere in the later period.

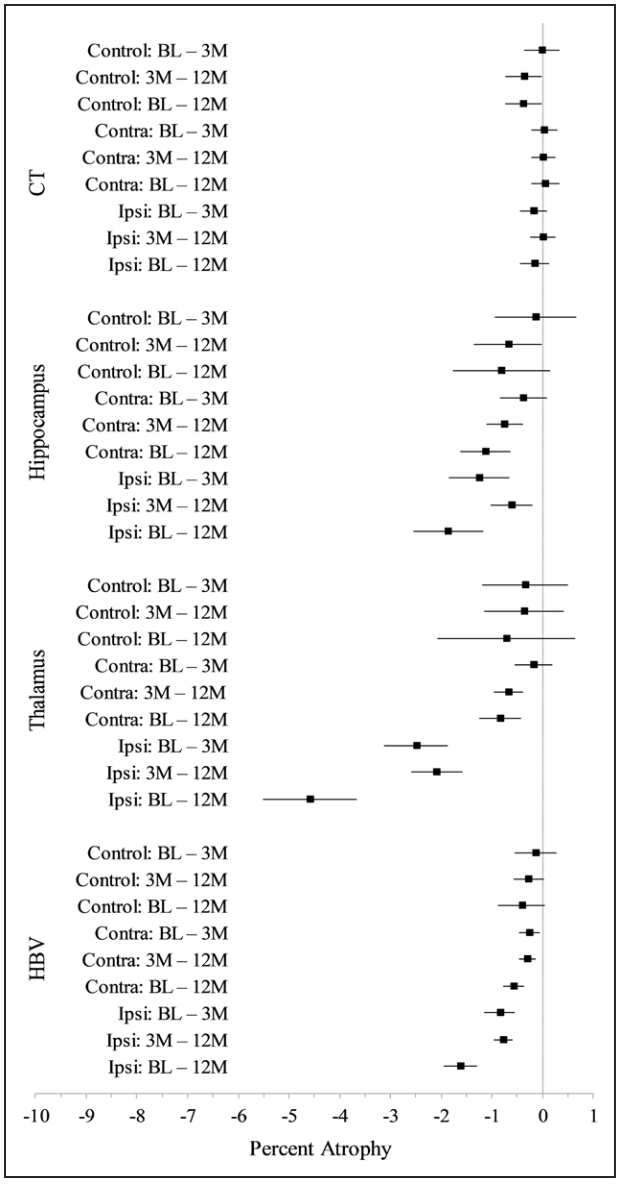

Figure 2. Forest plot of within-group amount of atrophy (%) over each time period for stroke participants.
BL indicates baseline; Contra, contralesional; CT, cortical thickness; HBV, hemispheric brain volume; Ipsi, ipsilesional; and M, months.

Hippocampal Atrophy

Ipsilesional early rate of atrophy was much greater than the later rate (0.64 mm^3/d cf. 0.08 mm^3/d), and percent atrophy was significantly greater than the control group over the early period (1.25%). Contralesionally, the early period rate of atrophy (0.19 mm^3/d) was significantly greater than the later period (0.1 mm^3/d, Figures 3 and 5). Contralesional volumes were not significantly smaller than controls at any each time point, but percent atrophy

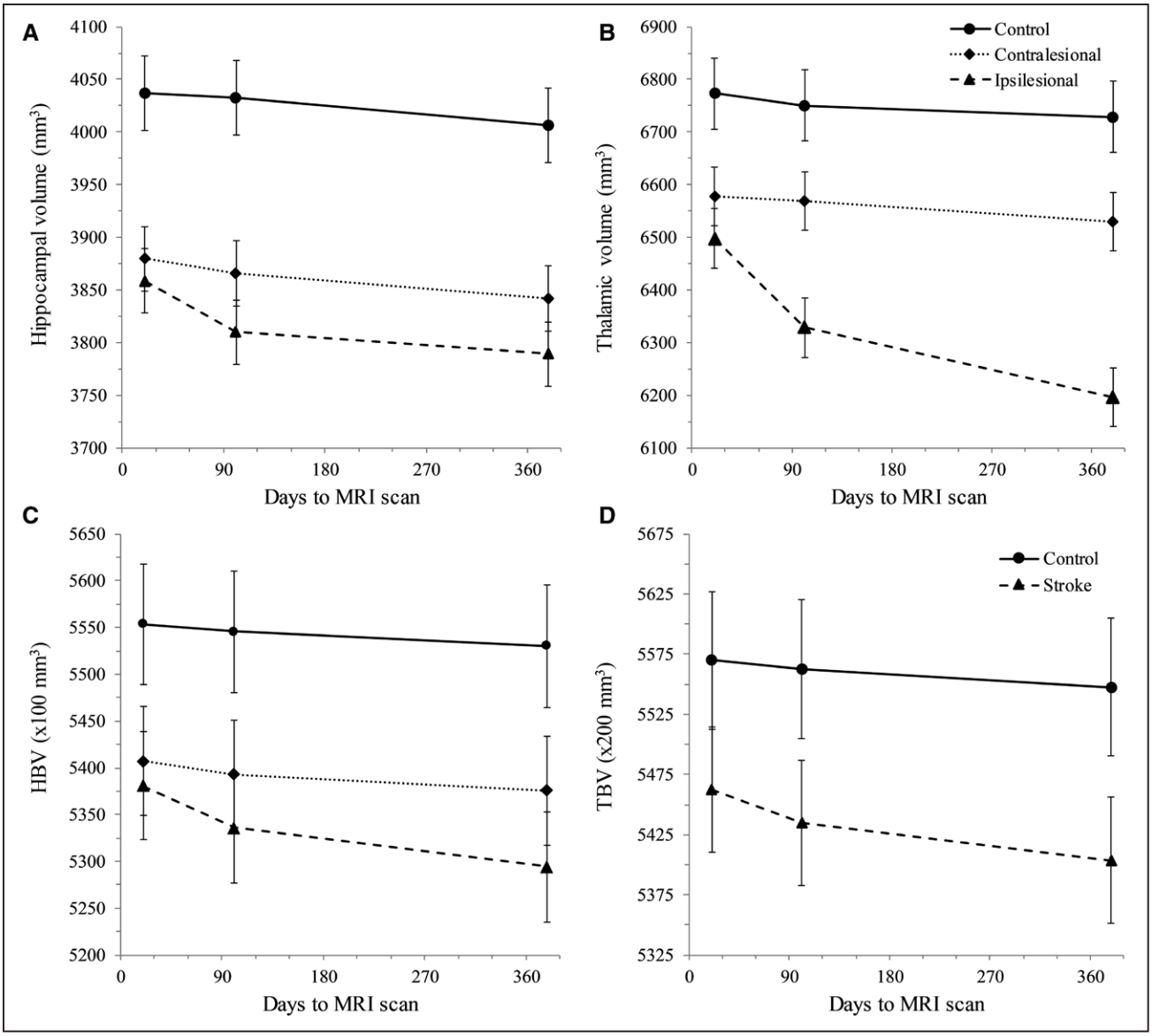

Figure 3. Brain volume trajectories.

AQ8 **A**, Hippocampal, (**B**) thalamic, (**C**) hemispheric brain (HBV), and (**D**) total brain volumes (TBV) at each time point (*x*-axis shows days to magnetic resonance imaging [MRI] scan) with SE bars.

was significantly greater in both the later and full periods (0.75% and 1.12%, respectively).

Thalamic Atrophy

Ipsilesional percent atrophy was 2.5% in the early period, 2.09% in the later period, and 4.59% overall. These reductions were all significant and were significantly higher than within-control reductions over all 3 periods (Figures 3 and 5). They were also significantly higher than contralesional reductions over the early and full time periods. The ipsilesional early rate of atrophy (2.14 mm^3/d) was nearly 4.5× faster ($P<0.001$) than the later-period atrophy rate (0.48 mm^3/d). The ipsilesional volumes were also significantly lower than their counterparts in control at 3 and 12 months. Contralesional volumes were not significantly smaller than those in control at any time point. Contralesional rates of atrophy were similar over all time periods, yielding a 0.16 mm^3/d average rate (Figure 5), and were not significantly different from those in controls over any time period.

Cortical Thickness Reduction

Contralesional cortical thickness, percent change, and rates of atrophy in stroke were not significantly different from those in controls (Figures 2, 4, and 5; Table V in the Data Supplement).

We repeated these analyses excluding those participants whose APOE status was not known. These results mirror our original results, although interestingly, control and contralesional atrophy amounts are overall less while ipsilesional atrophy is higher (Table II in the Data Supplement). Assuming that APOE ε4 carriers would exhibit

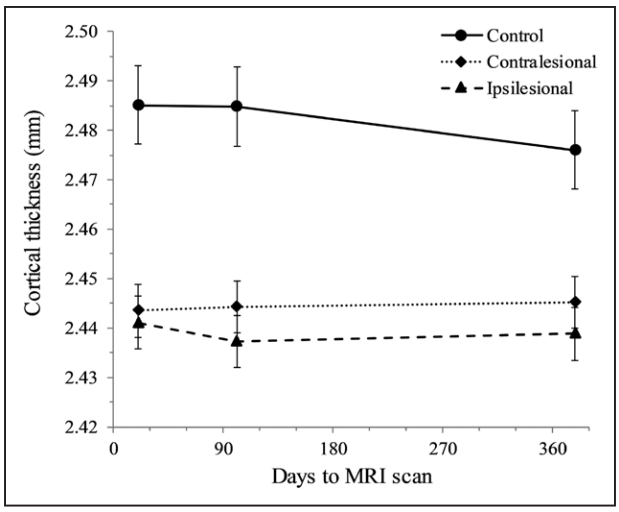

Figure 4. Cortical thickness trajectories.
Mean cortical thickness shown at each time point for control and stroke participants with SE bars. MRI indicates magnetic resonance imaging.

worse atrophy, these findings suggest that participants with missing APOE status were probably mostly not ε4 carriers since their inclusion resulted in slightly lower atrophy. Also, the rates of cortical thickness change for controls were closer between the 2 time periods and remained not significantly different.

DISCUSSION

We report significant reductions in selected regional brain volumes in the first year after clinical stroke. We found that (1) baseline volumes did not differ significantly between stroke patients and controls using the longitudinal FreeSurfer stream; (2) ipsilesional reductions in volumes occurred in all regions from baseline to 3 months; (3) late ipsilesional reductions continued to occur from 3 to 12 months in total brain, hemispheric brain, and thalamic volume; and (4) ipsilesional hemispheric brain volume loss was greater than contralesional over each time period, but both hemispheres atrophied over the 12 months. These early changes are occurring over the peak stroke recovery period, where whole-brain remodeling has been described, both contralesionally and in extant perilesional cortex.[25] This contrasted with control participants, whose atrophy rates for all metrics did not differ between time periods. Their rates were consistent with prior healthy brain aging studies, in which rates of brain volume change did not vary considerably over one year, with reported annual TBV decreases of 0.2% to 0.6%.[26,27]

Differences in the rates of atrophy suggest a direct effect of the stroke lesion itself. The expansion or shrinkage over time of the stroke lesion may have played a role in the determination of regional volumes and rates of atrophy. This is especially true for hemispheric and TBV since chronic stroke lesions, seen as hypointense on magnetization-prepared rapid gradient (T1 weighted) images, are fully embedded in the area used for TBV estimation. Cortical thickness was an exception to this generalization, with no differences between the groups at any time point. Dynamic changes in this time period have been described, including cortical thickness

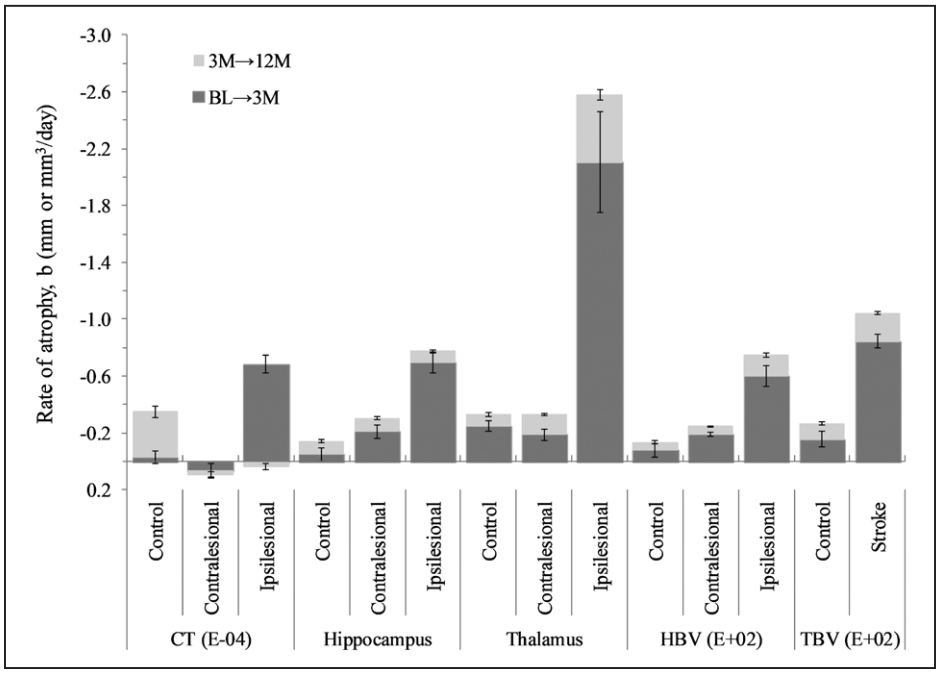

Figure 5. Daily rate of brain volume change at early and later time periods.
Rate of brain volume change during early and later time periods. Rate of atrophy (mm/d for cortical thickness (CT) and mm³/d for total brain volume (TBV), hemispheric brain volume (HBV), hippocampus, and thalamus during the early and later time periods shown with SE bars (3M indicates 3 months; and BL, baseline).

increases, which could have affected our measures.[16,28] This is at odds with reports of cortical thinning overlying subcortical infarcts and in connected regions remote from the infarct.[29] However, we did not perform specific subregional cortical analyses, and it is very possible that such regional thinning could have been missed via our hemispheric model. Cortical thinning may be a manifestation of preexisting microvascular disease, as has been extensively reported in hypertensive populations.[30]

Hippocampal and thalamic percent changes in our stroke participants are clearly greater than those in controls. Barnes et al[31] reported mean annualized hippocampal atrophy rates of 4.66% (CI, 3.92%–5.40%) for AD participants and 1.41% (0.52%–2.30%) for healthy controls in their meta-analysis. Our thalamic volume reduction (0.69%) over the full period in controls is comparable to the annual thalamic atrophy reported in healthy aging.[26] Our finding of a 4.9% reduction in ipsilesional thalamic volume is much greater than the 1.5% annual thalamic atrophy reported for AD,[26] perhaps reflecting the impacts of disconnection and selective regional vulnerability. In addition, ipsilesional hemispheric volume reductions are greater than those reported in either hemisphere in AD. These atrophy rates suggest accelerated neurodegeneration.

There are several possible contributors to the observed regional volume loss. Degeneration remote from an infarct site is well described, usually ascribed to Wallerian degeneration from cortical disconnection to regions, such as the thalamus and substantia nigra.[32] Diffusion MRI has revealed chronic changes in the ipsilesional hemispheric white matter[33] and thalami.[34] Ongoing degeneration in the corticospinal tracts and thalami has been described years after stroke, suggesting that accelerated brain atrophy continues to occur as a result of the infarct.[35] Thalamic microglial activation and neuronal number decrease have been observed in a network-based manner in rodent stroke models, suggesting that white matter inflammation plays an integral role in this remote degeneration.[36]

Ongoing neurodegeneration in the limbic system after stroke has also been described. Haque et al[37] reported that cingulate cortical thickness was significantly decreased at 12 months, with associated white matter tract degeneration. Reduced hippocampal volumes have been reported in cross-sectional imaging studies, and authors of postmortem studies have corroborated reduced pyramidal neuron volumes in poststroke and vascular dementia populations, independent of Alzheimer pathology.[38] Akinyemi et al[39] found no significant difference in hippocampal AD pathology in demented and nondemented poststroke subjects, nor any association with cognitive performance, and concluded that mechanisms other than amyloid may be driving neurodegeneration following stroke. Ouyang et al[40] found fewer neurons and more glia in the ipsilateral thalamus and hippocampus in primate middle cerebral artery occlusion induced stroke middle cerebral artery occlusion group at 12 months poststroke compared with a sham control group.

Neurodegeneration is usually considered a pathological process mainly associated with toxic brain protein species, such as AD and related dementias, and not primarily arising from vascular causes. Although Wallerian degeneration is believed to be the major factor underlying secondary neurodegeneration after stroke, it would not explain hippocampal volume loss, or cortical thinning per se and should be limited to the white matter atrophy reflected in our total brain and hemispheric volumes. We would argue that mechanisms other than Wallerian degeneration or atrophy associated with toxic brain proteins could underlie this neurodegeneration. We have previously published on the lack of association between cortical amyloid and stroke in a longitudinal series of ischemic stroke patients.[41] In the largest series to date, Hagberg et al[42] followed 208 stroke survivors over 7 years and found that amyloid binding was not associated with cognitive impairment. They did not find that cortical amyloid deposition correlated with other measures related to neurodegeneration or cognition, concluding that amyloid pathology may not be a key mediator of neurodegeneration poststroke. The lack of association between amyloid and poststroke secondary neurodegeneration was also been shown in the primate middle cerebral artery occlusion stroke model where animals were euthanized a year after stroke.[40] They found no extracellular β-amyloid plaques in the thalamus or hippocampus, but rather, found extensive, enduring secondary thalamic and hippocampal neuronal loss in association with extensive microglial activation in these regions.[40]

We have shown that pervasive white matter degeneration occurs within 3 months after stroke—more than could be explained by Wallerian degeneration alone[43]—and that network-dependent cortical degeneration is occurring.[44] Duering et al[17,29] have also shown cortical thinning over acute ischemic infarcts. Cheng et al[45] have shown cortical thinning in areas connected to ischemic lesions as well as homologous contralateral brain regions, which they posited may be driven by transcallosal diaschisis. Our observations may have implications for the understanding of the competing influences of structural reorganization and degeneration after stroke.

We have previously demonstrated gray and white matter volume loss after stroke, both within connected networks, and remote from the stroke site, suggesting pervasive neurodegeneration.[3,16,44] The concept of primary vascular neurodegeneration is gaining currency, with some researchers positing that vascular dysregulation is the driver of atrophy, cognitive decline, and incident vascular events.[46] We would argue that the main driver of secondary neurodegeneration is neuroinflammation. Enduring microglial activation has been described in rodent and primate models. Inflammation has both critical early beneficial and later detrimental effects, influencing remodeling, and repair. Several

preclinical and proof-of-concept studies have targeted inflammation poststroke, including to improve poststroke recovery. These agents could also potentially affect poststroke secondary neurodegeneration. Regional brain atrophy rates could serve as biomarkers for future trials.

Strengths and Limitations

The strengths of this study lie in its prospective design, standardized imaging (all performed on a single scanner), and robust sample size, including both people with stroke and their age- and sex-matched controls. We included all ischemic stroke types and sites. Despite having broad inclusion criteria for stroke types, many participants were excluded on the basis of other exclusion criteria, such as chronic health issues, prior cognitive impairment, and MRI incompatibility, such as claustrophobia or implanted metal. One weakness is its lack of postmortem data. Molecular imaging for tau, amyloid, or neuroinflammation would have also been useful. In addition, despite attempts to include a broad range of stroke subtypes, we had a relatively mild stroke cohort. Obviously, no prestroke imaging was obtained, impossible for this study design. Blinding remains problematic when analyzing imaging data because of the presence of the stroke lesion, but we made every attempt to keep our imaging analyst blinded to participant status. Control participants had more years of education and higher National Adult Reading Test-FSIQ than our stroke participants: a common problem with volunteer bias. We were only able to examine 2 time periods within the first year. Ideally, multiple imaging time points would have been included to tease apart the trajectories of brain volume change after stroke, and to allow disentanglement of the effects of preceding vascular risk and the intercedent stroke. These sorts of studies are both expensive and burdensome to our patient populations. However, we know from rodent studies that microglial activation and neuroinflammation are widespread after infarction,[47] and pinpointing the time of peak inflammation—and subsequent neuronal loss and atrophy—would be of great use in designing intervention trials to target inflammation and promote neurogenesis.

SUMMARY

We conclude that rapid decline in total and regional brain volume occurs early after stroke, with ongoing accelerated atrophy rates compared with controls. Brain atrophy rates could serve as a useful biomarker for future intervention studies to prevent poststroke brain volume loss and future cognitive decline.

ARTICLE INFORMATION

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Disclosures

None.

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