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# Changes in regional brain volume three months after stroke

Amy Brodtmann [a,b,*], Heath Pardoe [a,b], Qi Li [a], Renee Lichter [a,b], Leif Ostergaard [c], Toby Cumming [a,b]

[a] Florey Neuroscience Institutes, Melbourne Brain Centre, 245 Burgundy Street, Heidelberg, 3081, Australia
[b] University of Melbourne, Parkville, 3050, Australia
[c] Aarhus University, Copenhagen, Denmark

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ABSTRACT

*Introduction:* Little is known about changes in regional brain volume after stroke. We investigated cortical thickness changes over 3 months in a group of stroke patients compared with controls.
*Material and methods:* Patients with acute hemispheric stroke were studied within 3 h of stroke onset and serially over 3 months. We compared the acute and 3 month scans with independently acquired control images. High resolution isotropic T1 images were analyzed using FreeSurfer V5.0, comparing regional average cortical thickness, hippocampal and thalamic volumes. Stroke patient results were analyzed separately for ipsilesional and contralesional regions, whereas control results were averaged across hemisphere. Percentage change scores between the two time points were computed for each participant, and paired sample t-tests were used to assess significant change.
*Results:* 12 stroke patients (9 men, 7 left-hemispheric, mean age = 65.1 years) and 10 control participants (5 men, mean age = 67.2 years) were included. There were no significant differences between the 2 time points in global or regional average cortical thickness, or hippocampal and thalamic volume estimates for control subjects. Regional variability in patient data was demonstrated, particularly cortical thickness increases in contralesional paracentral, superior frontal and insular regions, areas known to be activated in functional MRI studies of motor recovery. A significant reduction in thalamic volume was also found, most apparent ipsilesionally.
*Conclusions:* Post-stroke changes in regional cortical thickness are demonstrable even over short time-frames. Contralesional cortical thickness increases may represent compensatory mechanisms. Significant reductions in thalamic volume may represent evidence of early post-stroke atrophy. Further studies are required to confirm and extend these preliminary results.



## 1. Introduction

### 1.1. Post-stroke reorganization

Significant dynamic reorganization of distributed networks is well described after stroke, especially in the functional neuroimaging literature [1–3]. This reorganization has been described in the visual [4], language [5], attention and sensory networks [6], but the majority of researchers have focused on motor recovery and associated motor cortical regions due to the importance of motor recovery to functional independence [7]. Activation patterns are usually characterized by early utilization of homologous regions in the contralesional (intact) hemisphere (contralesional recruitment) [1–3], followed by expansion of cortical representation of the damaged area of the cortex into adjacent areas (peri-infarct), with subsequent activation of other cortical and sub-cortical regions distant to the lesion [2,8–10]. There is strong evidence that restitution of activation to the ipsilesional hemisphere is associated with a better functional outcome, particularly in the chronic post-stroke phases [2,3,11]. Most of these studies have used positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques to document changes, but more recently methods such as diffusion tensor imaging and connectivity analyses have been used [12–16].

### 1.2. Cortical thickness changes after stroke

Cortical thickness estimates have been used to document dynamic changes in the human brain, both in normal learning and in pathological states, particularly neurodegenerative processes such as Alzheimer's disease (AD) and frontotemporal dementia. Researchers have reported significant regional volume increases in people intensively learning new tasks, such as London cab drivers learning the maps of London [17,18], melody recognition in expert musicians [19], and students acquiring expertise in a new language [20]. Surprisingly, cortical thickness analyses have not been used to chart cortical plasticity after stroke,

* Corresponding author at: Florey Neuroscience Institutes, Melbourne Brain Centre, 245 Burgundy Street, Heidelberg 3084, Australia. Tel.: +61 3 9035 7004; fax: +61 3 9035 7404.
*E-mail address:* agbrod@unimelb.edu.au (A. Brodtmann).

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despite the fact that there is strong evidence that such functional changes are taking place. There is now some evidence that regional volumes may decline in the long-term after stroke, particularly in patients who subsequently develop cognitive decline [21,22].

### 1.3. Atrophy and cognitive decline

Recent research has indicated that consistent patterns of regional cortical thickness change are strongly associated with AD [23–25]. There is now a large body of work examining the association between brain volume changes and disease diagnosis and progression in many dementia syndromes. There is evidence from animal models that cortical thickness changes occur in the post-stroke period. Using a rat stroke model, Karl et al. found decreases in cortical thickness, volume, and neural density extending far beyond the stroke infarct [26]. There is evidence in humans that some brain regions—such as hippocampi and thalami—exhibit disproportionate atrophy after stroke [27,28].

Cognitive impairment and dementia are common after stroke [29], with vascular dementia accounting for about one-fifth of all dementia cases [30]. Yet we still know very little about whether brain volume loss—a hallmark of dementia—occurs after stroke, and whether such atrophy is related to cognitive decline. Magnetic resonance imaging (MRI) markers of structural brain aging (such as lower total brain volume, hippocampal volume or increasing white matter hyperintensity load) and performance on neuropsychological tests of memory and executive function are powerful predictors of dementia in the general population [31–34]. In contrast to pathologically-based autopsy studies, using brain volume measures to investigate the association between stroke and dementia permits a longitudinal approach.

### 1.4. Current study

Dynamic remodeling after stroke may lead to changes in cortical thickness, but these have not been demonstrated. Minimal evidence hints at some post-stroke regional atrophy, but this is also unclear [21,22,28]. Despite the hundreds of longitudinal stroke studies using MRI, there have been no reports of cortical thickness analyses using high-resolution regional estimates such as FreeSurfer [35,36]. We performed an exploratory analysis of cortical thickness changes in order to address the feasibility of volume comparisons between the hyperacute post-stroke periods and more chronic time points. We investigated cortical thickness changes over a 3 month period in both a group of stroke patients and healthy controls of a comparable age. We compared the regional volumes of patients studied acutely with their scans performed at 3 months post-stroke. We hypothesized that there would be a decline in the regional volume of the hippocampi and thalami of stroke patients, but did not expect significant cortical thickness changes in either stroke or control participants over this short time frame.

## 2. Materials and methods

### 2.1. Participants

Patients were prospectively recruited into a thrombolysis study using MRI imaging in the acute and chronic post-stroke periods to establish recanalization rates (author L.O.). They were included if: they presented with a first-ever acute middle cerebral artery (MCA) territory stroke, were able to be studied with MRI within 2 h of stroke onset, were previously independent without cognitive decline, and were able to be scanned over a 3 month period. Patients were studied within 2 h and serially over 3 months (at study inclusion, 3 h, 24 h, 1 week, 6 weeks and 12 weeks). We compared the 2 hour and 3 month scans with independently acquired control images, also taken 3 months apart. Healthy control participants were included if: they were aged 60–90 years, had no prior neurological or significant psychiatric disease, had no significant carotid artery stenosis on carotid duplex Doppler ultrasound, and no stroke on MRI.

### 2.2. Imaging

Patients: 12 patients were scanned. 10 patients had 3D T1-weighted whole brain FSPGR images acquired on a GE Signa Excite 3 T MRI scanner with the following acquisition parameters: echo time TE = 3 ms, repetition time TR = 625 ms, flip angle = 20°, voxel resolution = 0.9375 mm in plane, slice thickness = 1.3 mm. Two stroke patients were scanned on a GE Genesis Signa 1.5 T MRI scanner: TE = 4.2 ms, TR = 830 ms, flip angle = 20°, voxel resolution = 0.9375 mm in plane, slice thickness = 1.5 mm.

Controls: 3D T1-weighted whole brain MPRAGE images were acquired on a Siemens TRIO MRI scanner with the following acquisition parameters: echo time TE = 2.55 ms, inversion time TI = 900 ms, repetition time TR = 1900 ms, flip angle = 9°, voxel resolution = 1 mm isotropic.

### 2.3. Analysis

The structural scans were processed using FreeSurfer V 5.0 with default processing settings. Processed images were visually inspected and skull stripping and white matter edits were made where appropriate. Cortical thickness measures were averaged at the lobar level using the inbuilt FreeSurfer cortical parcellation procedure (“aparc”). FreeSurfer produces cortical thickness maps of 35 cortical regions (measured in millimeters) as well as volume estimates of structures, including the thalami (in $mm^3$).

We compared average cortical thickness in each of the cortical regions as well as hippocampal and thalamic volumes. For stroke patients, results were divided into ipsilesional and contralesional regions, in order to compare stroke hemisphere with non-stroke hemisphere. To identify whether stroke severity was related to brain volume change, correlations were computed between acute National Institutes of Health Stroke Score (NIHSS) score and volume measures. For controls, cortical thickness and volume measures were averaged across left and right hemispheres. Paired-sample t-tests were used to establish whether the measures of brain volume changed significantly over 3 months.

Given the differences in regional thickness between individuals, particularly with increasing age, we elected to use change scores rather than absolute values. This was done to minimize the problems associated with cortical thickness differences that occur as part of normal aging [25,37]. To account for individual variability in baseline volumes, baseline and 3 month data were used to compute percentage change scores for each participant. Group differences in mean percentage change score were analyzed using independent t-tests. The significance level of $\alpha = 0.05$ was not adjusted for multiple testing, and results from this preliminary study should be interpreted with this in mind.

Individual images were inspected to check the accuracy of the automated segmentation. Given the very acute time frame of the first imaging session, the stroke site was barely visible, as ischemic infarction in the hyperacute setting is not associated with the accumulation of significant edema. The presence of edema becomes problematic in the 24–72 hour period, hence the choice of the 2 hour scan for the comparison. We performed the analyses with the lesions unmasked, particularly given only 2 were cortical. Qualitative inspection of the cortical thickness results showed that the modeling of the gray/white matter and outer gray matter surfaces exterior to the lesion was unaffected by the presence of the lesion.

## 3. Results

Twelve stroke patients (9 men, 7 left-hemispheric, mean age = 65.1 years, range 45–74 years) were included. Ten strokes were