Default mode network neurodegeneration reveals the remote effects of ischaemic stroke

INTRODUCTION
Dementia is estimated to occur in 15%–30% patients after ischaemic stroke. Stroke may initiate or accelerate neurodegeneration associated with cognitive impairment. Brain atrophy is an important marker of neurodegeneration, preceding the emergence of cognitive symptoms in Alzheimer’s disease (AD). Atrophy occurs in distributed regions that collectively mirror known brain networks, including the default mode network (DMN). Atrophy and dysfunction within the DMN is evident in healthy ageing, accelerated in pathological ageing and evident in acute and subacute stroke. Lesion location rarely predicts long-term outcome in stroke. Network-wide changes may better explain neurodegeneration and conversion to dementia after stroke. Atrophy after stroke has not been well investigated and has been limited to cross-sectional studies and regional volume changes.

Structural covariance is an increasingly popular method of examining network-wide correlations in morphometric estimates of brain structure, such as cortical thickness or grey matter volume. There is a close relationship between estimates of network-based structural covariance and intrinsic functional network architecture. Structural covariance can be tracked over time to reveal changes in brain organisation, either developmental or degenerative, via cross-sectional comparisons within and between groups. Cross-sectional differences can be difficult to detect when there is normal variability across individuals. Longitudinal imaging has the benefit of overcoming interindividual differences in cortical morphology by using each individual as their own control. Longitudinal imaging also provides an opportunity for more direct examination of atrophy within networks by looking at correlations in the rate of cortical atrophy across the left hemisphere, relative to the PCC seed, revealed several regions within the DMN with covarying atrophy, including the posterior cingulate, parahippocampal gyrus and medial frontal gyrus in patients with stroke (figure 1). In healthy controls, correlated atrophy was seen in the posterior cingulate, medial and superior frontal gyrus and the precuneus, suggesting age-associated atrophy. Although qualitatively it appeared that the healthy controls had more regions of atrophy, a direct contrast of patients who had stroke compared with healthy controls showed more extensive atrophic covariance in patients who had stroke. The reverse contrast showed no regions of atrophy beyond the DMN, encompassing the middle temporal gyrus and the insula.

METHODS
Participants
We analysed 3-month and 1-year data from the Cognition and Neocortical Volume after Stroke study that includes neuropsychological assessment and MRI scanning in repeated sessions over 3 years. Patients and healthy control participants gave informed consent, and ethical approval was granted by each hospital’s human research ethics committee in line with the Declaration of Helsinki. Only non-demented participants with ischaemic stroke were included. The study procedure and image acquisition details are available in the protocol.

Image processing
Structural T1-weighted images were processed using the longitudinal stream in FreeSurfer V.5.3. The longitudinal stream creates an unbiased within-subject template, which becomes the reference image for registrations, segmentations and surface reconstructions for images from each time point. Stroke lesions were manually traced on the fluid-attenuated inversion recovery image at the 3-month time point only, independently verified by stroke neurologist (AB) and converted to a surface-based lesion mask. The lesion mask was used to exclude damaged regions from longitudinal cortical thickness estimations to prevent bias and underestimation as a result of the stroke lesion itself. A seed region of interest was created as a 4 mm sphere around peak coordinates (−2,−54, 27, MNI space) within the posterior cingulate cortex (PCC) and projected onto the cortical surface using an inbuilt FreeSurfer functions. As this 4 mm sphere fell within the left hemisphere and the majority of strokes were in the right hemisphere, cortical thickness estimates were restricted to this side (see figure 2 in the online Supplementary file 1 for stroke overlap map). Vertex-wise Pearson’s correlations in the rate of atrophy were calculated relative to the posterior cingulate seed in both groups.

RESULTS
We analysed data from 53 patients who had stroke (mean age 67 years, SD 12) and 21 healthy, age-matched controls (mean age 68 years, SD 6). Demographic details are reported in table 1 in the online Supplementary file 1). Importantly, there were no significant differences between groups in mean age or the number of days between scans (t(15.82)=−0.75, p=0.47). The stroke group had significantly lower mean MoCA scores at 6 weeks poststroke compared with healthy controls (t(40.68)=3.47, p<0.001).

Vertex-wise correlations in the rate of cortical atrophy across the left hemisphere, relative to the PCC seed, revealed several regions within the DMN with covarying atrophy, including the posterior cingulate, parahippocampal gyrus and medial frontal gyrus in patients with stroke (figure 1). In healthy controls, correlated atrophy was seen in the posterior cingulate, medial and superior frontal gyrus and the precuneus, suggesting age-associated atrophy. Although qualitatively it appeared that the healthy controls had more regions of atrophy, a direct contrast of patients who had stroke compared with healthy controls showed more extensive atrophic covariance in patients who had stroke. The reverse contrast showed no regions of atrophy beyond the DMN, encompassing the middle temporal gyrus and the insula.

DISCUSSION
We show correlated atrophy in regions of the DMN after focal ischaemic stroke. This atrophy was more extensive than is seen in normal ageing demonstrating...
remote effects of stroke across the brain, including in seemingly healthy tissue that is distant from the lesion site. Stroke location is a poor predictor of cognitive impairment. Examining the networks effects of stroke may help to clarify the neurodegenerative pathway that leads to poststroke dementia.1

Atrophy within DMN nodes is seen in healthy ageing and appears to be accelerated in pathological ageing.2 Singh et al,2 demonstrated progression of atrophy of key nodes within the DMN, in mild cognitive impairment that extended into the medial, superior frontal and parahippocampal gyri in AD. These same regions were affected in our stroke group, where atrophy was also more extensive than seen in normal ageing. Neurodegenerative dementias target intrinsic functional networks, with the spatial pattern of atrophy closely reflecting the spatial distribution of regions within relevant functional networks. We provide evidence of correlations in the rate of atrophy within key regions in the DMN that suggests the pattern of atrophy does mirror DMN functional disruption seen after stroke.3

We present a new longitudinal method for examining atrophy within functional networks. By examining correlations in the rate of cortical atrophy, rather than the measure of cortical thickness itself, we can more directly show the degeneration of networks over time.

A limitation to our study is that at the time of assessment, patients had minimal deficits. Despite this, we found significant changes in brain network atrophy, furthering the concept of network-wide degenerations in this relatively ‘mild’ cohort. Future work will relate atrophy directly to cognitive outcomes to further characterise the impact of network degeneration after stroke.

CONCLUSIONS

We showed correlations in the rate of atrophy within the DMN, which is more extensive after ischaemic stroke, reflecting pathological network-wide neurodegeneration. Network-wide atrophy after stroke may help to clarify the neurodegenerative trajectory from focal ischaemic stroke to poststroke dementia.

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