Serial Quantitative Atlas-based MRI Volumetry to Assess Progressive Neocortical Damage in Epilepsy

R. S. Liu¹, L. Lemieux¹, A. Hammers¹, G. S. Bell¹, S. M. Sisodiya¹, S. D. Shorvon¹, J. W. Sander¹, J. S. Duncan¹
¹Institute of Neurology, London, London, United Kingdom

Synopsis
We investigated the pattern of generalized and focal neocortical atrophy that develops in patients with epilepsy. Patients and controls were scanned 3.5 years apart. Image subtraction was used to identify neocortical change that was quantified by automatic segmentation and a regional brain atlas. New focal or generalized neocortical volume losses were identified in 54% of patients with chronic epilepsy, 39% of newly diagnosed patients and 24% of controls. The increased risk of cerebral atrophy in epilepsy was not related to a history of documented seizures. Cerebral atrophy may therefore be widespread and remote from the epileptic focus.

Introduction
Cross-sectional quantitative volumetric MRI studies of epilepsy have inferred that the hippocampus, cerebellum, temporal lobe, extratemporal cortical region and cerebral hemisphere are susceptible to volume loss [1-2]. Whether a correlation between seizure frequency and extrahippocampal volume deficit exists is unclear. Longitudinal studies with serial MRI scans allow the quantification of morphological change over time, using an individual’s baseline scan as a reference point. Quantitative MRI studies investigating brain volume changes in epilepsy have generally used region-based methods. Such methods, however, restrict analyses to a priori interest. We propose a voxel-based analysis method using automatic coregistration, subtraction and segmentation of serial MRI scans and quantification of focal changes of grey matter (GM) and white matter (WM) using a digital atlas.

Methods
153 patients with chronic active epilepsy, 90 patients with newly diagnosed seizures and 90 age-and sex-matched control subjects were prospectively recruited from a local population of 207,553. Subjects were scanned on a 1.5-T GE Signa Horizon Echospeed MR scanner (GE Medical Systems, Milwaukee, WI). Three experienced epileptologists classified patients at the time of recruitment according to epilepsy syndrome based on seizure semiology and EEG findings. Of the original cohort, 122 patients with chronic active epilepsy, 68 patients with newly diagnosed seizures and 90 controls were subjected to the follow-up assessment: scanning performed on the same MRI scanner using identical MRI acquisition sequences to the baseline imaging protocol (see below) and clinical data collection.

Volumetric measurements were derived from a T1-weighted volumetric inversion recovery prepared spoiled gradient echo (IR-SPGR) coronal sequence, giving 0.93x0.93x1.5mm³ voxels. Prior to volumetry, baseline and repeat T1-weighted volume datasets were corrected for signal inhomogeneity [3]. The automatic segmentation software program, Exbrain was used to extract the brain in the non-uniformity corrected baseline scan [4-5]. The repeat scan was coregistered and intensity matched to the segmented baseline scan using MRreg [6-7]. The coregistered repeat scan was subsequently resampled using sinc interpolation. Exbrain was used to segment the coregistered image pairs giving GM and WM probability maps [5]. Difference images of the whole brain were generated by subtracting the baseline from the coregistered and intensity-matched repeat scan, spatially normalisation and filtering with a structured noise map to remove changes due to physical artifacts. The structured noise map was derived from the difference images of 40 healthy adults scanned 7 months apart. Two observers rated the resulting filtered difference images, blinded to all clinical information, for change as either: mild, moderate or marked. Quantitative analysis was restricted to areas of signal change highlighted by visual assessment, using a probabilistic anatomical atlas obtained by the spatial normalisation of 20 atlases of normal subjects comprising 49 manually delineated volumes of interest, grouped into 8 regions for our purpose: right and left frontal, occipital and parietal lobes [8]. The template was spatially transformed into each individual MRI space. Application of the atlas to the segmented images resulted in baseline and repeat GM and WM volumes within the regions of interest.

Results
Individual analysis. The following figures exclude cases obscured by imaging artifacts. New focal or generalized neocortical volume losses were identified in 54% of patients with chronic epilepsy, 39% of newly diagnosed patients and 24% of controls. In the newly diagnosed group, 11% of patients showed a focal neocortical volume loss, 27% showed a generalized volume loss and 2% showed a generalized volume gain. In the chronic group, focal neocortical volume loss was identified in 14% of patients and 41% showed a generalized volume loss, and 2% showed a generalized gain in volume. Loss in TBV associated with mild generalized visual changes was [0.2 - 3.3%] and [1.4 - 4.3%] for moderate visual change. Temporal lobe volume losses in temporal lobe GM were [3.6 - 27.3%] and [5.3 - 26.9%] for WM. Frontal GM losses were [0.3 - 7.4%], and WVM losses [1.1 - 18.8%]. Four percent of patients with chronic TLE without hippocampal sclerosis (HS) and 17% with chronic TLE and HS developed extrahippocampal atrophy. None of the patients with newly diagnosed TLE and 2% of control subjects developed temporal lobe atrophy.

Group analysis. Patients with chronic epilepsy were significantly more likely to develop neocortical atrophy than control subjects. The pattern of change was significantly associated with baseline age and AED exposure during the follow-up period. The increased risk of cerebral atrophy in epilepsy was not related to a history of documented seizures. Risk factors for neocortical atrophy were age and multiple antiepileptic drug exposure.

Discussion and Conclusions
We have proposed a novel approach to the detection and quantification of subtle global and focal volume changes in serial MRI and applied it to a population-based study of the structural consequences of epilepsy. The approach is based on image registration, segmentation, visualisation of difference images and quantification of volume changes by the application of a VOI atlas. The proportions of subjects with neocortical volume loss were far greater in our current study identified than in our previous study on whole-brain and hippocampal volumetry [9-10], reflecting the new method’s superior sensitivity. Our findings suggest that focal and generalized neocortical atrophy commonly develops in chronic epilepsy; Changes seen in a quarter of our controls were likely to reflect physiological changes. Our results show that ongoing cerebral atrophy may be widespread and remote from the putative epileptic focus, possibly reflecting extensive networks and interconnections between cortical regions.

References