A longitudinal quantitative MRI study of community-based patients with chronic epilepsy and newly diagnosed seizures: methodology and preliminary findings

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Introduction

Experimental and human data suggest that progressive cerebral damage may result from the cumulative effect of brief recurrent seizures (1). Longitudinal studies addressing this fundamental question are, however, lacking. We have addressed this need with a large prospective community-based observational study, which aims to rescan 154 patients with chronic active epilepsy and 90 patients with newly diagnosed seizures, after an interval of 3.5 years. Here, we describe the quantitative magnetic resonance (MR) methods used to identify subtle volume changes in hippocampal (HC), cerebellar (CB) and neocortical structures over time and report preliminary findings. Using this methodology, we have previously shown (1) that we can reliably detect individual hippocampal volume (HV) and cerebellar volume (CBV) changes greater than 3.1% and 3.0% respectively.

Methods

To date, 53 subjects comprising 20 controls, 24 patients with chronic epilepsy and 9 patients with newly diagnosed seizures have undergone repeat MRI scans and are the subject of this report. Baseline and follow-up scans were performed on the same 1.5T GE Horizon MRI scanner using identical scan acquisition sequences. For volumetry, a fast inversion recovery prepared 3D spoiled gradient echo (IR-SPGR), T1-weighted volume sequence TR/TE/TI/NEX, 17.4/4.2/450/1; flip angle = 20°, matrix size = 256X192, 24X18cm FOV; 124 contiguous 1.5mm thick slices. Non-uniformity correction was performed using the automatic method, N3 (2), followed by automatic segmentation of the corrected scans (3, 4), resulting in an accurate delineation of the brain and cerebrospinal fluid (CSF). The repeat scan was then co-registered and intensity matched to the segmented baseline scan (5). Hippocampal volume measurements of both baseline and follow-up scans were performed using a mouse-drive cursor in consecutive slices of the both datasets of each subject displayed side-by-side. Patient and control data were randomly intermixed and the operator was blinded to the clinical status of the subject and whether the dataset displayed in the left-hand window was the baseline or the follow-up scan. The completed traces of the hippocampus in the left window were displayed whilst the hippocampal measurements were performed in the right window. For the purpose of identification of atrophy at baseline, baseline volumes were corrected for intra-cranial volume. Cerebellar volume measurements were semi-automated and performed on the matched segmented coronal images using the seed and region-growing method. The observer was blinded to the chronological order of the scan pair and the subject status. Seeds were deposited in the cerebellum, and the borders between the cerebellum and cerebrum, and cerebellum and brainstem were manually drawn. Measurements were performed on alternate slices, progressing in a rostro-caudal fashion with sagittal reconstructions displayed simultaneously to clarify anatomical orientation. The completed traces of the cerebellum were displayed on the left window whilst measurement of the matched segmented scan were performed in the active trace in the right window. For T2 relaxometry, the sequence was: 5mm thick contiguous oblique coronal proton density and T2 weighted spin echo images orthogonal to the long axis of the hippocampi, TR/TE 2000/30 (proton density), 2000/120 (T2-weighted). Measurements were performed on contiguous tilted coronal slices perpendicular to the longitudinal axis of the hippocampi. On average, the hippocampus was visible on 4-6 slices. The largest possible elliptical region of interest was placed in each hippocampal slice, avoiding partial volume effects from the CSF. Any change exceeding the mean control change plus or minus 2 times the standard deviation (SD) of the difference was considered significant.

Results

Recurrent seizures had occurred in 87.5% of patients with chronic active epilepsy and 33.3% of patients with newly diagnosed seizures. HV changes lying outside the normative ranges of -0.16cm3 to 0.088cm3 for the RHC and -0.12cm3 to 0.091cm3 for the LHC were considered significant. Normative ranges for the change in HT2 were -2.69 to +1.81 ms for the RHC and -2.21 to +1.86 ms for the LHC. The normative range for the change in CBV was -3.98cm3 to +5.25cm3. The normative range for the change in TVB was -44.8cm3 to +42.0cm3. Hippocampal volumetry identified 4 individuals with HV losses outside the normative range (see figure 1 for RHV). Significant reductions in CBV, TVB and GMV were detected in four, five and three individuals respectively. None of these volume changes had been previously detected on visual comparison.

Discussion

We describe the design and methodology of a prospective, blinded, longitudinal, quantitative MRI study to assess changes in the hippocampus, neocortex and cerebellum over a 3.5 year period. Of the 80 age-matched controls and 244 community-based patients with newly diagnosed seizures and chronic active epilepsy scanned between June 1995 and December 1997, we have so far obtained follow-up scans on 53 subjects. Using this technique of co-registration and intensity matching, we have minimized potential sources of bias in longitudinal studies, such as problems relating to variations in head position and scanner performance. The simultaneous display of the previously drawn hippocampal or cerebellar trace whilst performing the active trace is intended to improve the subjective aspects of volume measurements, especially when delineating the anterior part of the hippocampus. The potential concern that subtle biological changes might be masked by an imitation effect was dispelled in our previous pilot study comprising a blinded mixture of controls and patients, in which larger HV changes were detected in the patients (1). In conclusion, we propose that this methodology may act as a useful template for the design of longitudinal studies where the detection of subtle volumetric change is required.

References