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Automated quantitative FLAIR analysis in hippocampal sclerosis

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Summary
Purpose: To describe and evaluate a novel MRI post-processing technique for automated quantitative hippocampal FLAIR analysis in patients with hippocampal sclerosis (HS).
Patients and methods: Based on a method for FLAIR analysis presented by Focke et al. (2009), T1 and coregistered FLAIR scans of individual subjects were processed together in SPM5 to conduct both a spatial and an intensity normalization of the FLAIR scans. In a further development described here, the resulting normalized FLAIR images were thresholded and weighted by a probabilistic hippocampal mask to determine the average FLAIR intensities of left and right hippocampus. The method was applied to the MRI data of 103 HS patients and 131 controls. Using a 95% confidence region calculated from the FLAIR intensities of controls as threshold, the performance in discriminating both groups was assessed.
Results: One hundred of 103 patients and among those all 23 patients with histologically confirmed HS fell outside the 95% confidence region, amounting to 97.1% sensitivity. All but 6 controls (=95.4%) were found within the confidence region, corresponding to the expected specificity. The method could also distinguish bilateral HS and visualize signal changes after status epilepticus.
Conclusion: Automated FLAIR analysis is a promising tool to quantify hippocampal signal alterations, to support the detection of HS, and to monitor the temporal evolution of the disease.

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Introduction

Hippocampal sclerosis (HS) is the most frequent cause of pharmaocoresistant temporal lobe epilepsy (TLE) and the most common histopathologic diagnosis in patients with TLE undergoing epilepsy surgery (Urbach et al., 2004; Wiebe et al., 2001). The primary features of HS in magnetic resonance imaging (MRI) are atrophy of the hippocampus and hyperintense signal in fluid-attenuated inversion-recovery (FLAIR) and T2-weighted sequences (Jack et al., 1996; Jackson et al., 1990, 1993a). Visual detection of clear unilateral HS in good-quality MR images by experienced radiologists is considered unproblematic (Van Paesschen, 2004), but the recognition can be difficult for subtle sclerosis or cases of bilateral HS where a side comparison is hampered. In addition, subtle changes of T2 signal intensity over time, e.g. during potential progression of limbic encephalitis to HS, are difficult to assess by pure visual analysis. Focke et al. (2008, 2009) have recently described a new method for *quantitative* analysis of FLAIR scans, i.e. images with T2-weighted contrast but complete suppression of high signal intensity of cerebrospinal fluid (CSF). Their approach avoids difficulties due to partial volume effects with CSF which are to consider for other quantitative methods like T2 relaxometry. Compared to T2 mapping with FLAIR CSF suppression (Rugg-Gunn et al., 2005) it does not require a special FLAIR T2 map which has a long acquisition time and is often not available but takes a standard clinical FLAIR spin echo sequence as input. Essentially, the voxel-based method performs both a *spatial* and *intensity* normalization of FLAIR images by using internal reference regions and spatial normalization parameters derived from combined normalization and segmentation of a coregistered T1-weighted image (Focke et al., 2008, 2009). The normalized and rescaled FLAIR images are the starting point for a whole brain FLAIR analysis which has been shown to be successful in the detection of focal cortical dysplasia. In the present study, we describe a further development of this method for *regional* quantitative FLAIR analysis of the hippocampus and present first results in patients with HS compared to controls.

Methods

Patients and controls

At the Swiss Epilepsy Centre in Zürich, a register has been maintained for all patients receiving an MRI since January 2006. The majority of these patients had a high-resolution MRI at a Philips Achieva 3T scanner (Philips, Amsterdam, The Netherlands) according to a dedicated epilepsy protocol which comprised the following sequences: an unenhanced T1-weighted volume data set (3D Turbo Field Echo sequence with 1 mm^3 voxel; TR 8.1 ms; TE 3.7 ms; flip angle 8°; field of view 256 mm × 256 mm, slab thickness 160 mm; sagittal acquisition), axial and coronal FLAIR sequences (slice thickness, 3.3—6.1 mm and 2.6—2.8 mm, respectively; TR 11,000 ms; TE 120 ms; inversion time 2800; flip angle 90°; field of view 500 mm × 500 mm), a coronal T2-weighted fast spin echo sequence with 2 mm slice thickness, and axial T2*-weighted fast field echo and T1-weighted Gadolinium-enhanced spin echo sequences of 5 mm slice thickness. From this subgroup with MRI acquired at the same scanner and with the same protocol all patients with focal epilepsy were extracted in whom HS had been diagnosed in the past according to primary MRI criteria (i.e. atrophy, T2 hyperintensity, and loss of hippocampal lamination). In addition, all available subjects without epilepsy and without temporo-mesial pathology on MRI were taken as controls for the present study. Thus, controls with other neurological diseases or MRI pathology outside the region of interest were allowed. Exclusion criteria were gross movement artefacts in the T1-weighted volume data set or artefacts involving the temporo-mesial structures in the coronal FLAIR image (i.e. movement, pulsation, or susceptibility artefacts).

MRI post-processing

The first part of MRI post-processing in this study, i.e. the calculation of spatially and intensity normalized FLAIR images, was largely based on the method of whole brain FLAIR analysis as described by Focke et al. (2008, 2009), respectively. In its key step this method uses high-resolution T1 and coregistered FLAIR scans of an individual patient to conduct both a spatial as well as an intensity normalization of FLAIR scans in the framework of SPM5 (statistical parametric mapping software, Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). The intensity normalization is done by using an internal reference region (anterior frontal white matter and pons) and applying a correction factor to the raw image values (Focke et al., 2008). Further processing steps are spatial normalization to Montreal Neurological Institute (MNI) space, brain-masking with FMRIB Software Library's (FSL's) brain-extraction tool 'bet' and convolving with an 8-mm FWHM Gaussian kernel. Subsequently, an SPM5 general linear model is set up to compare each individual patient against a control group. An update of this method (Focke et al., 2009) includes an additional bias-correction step of the raw FLAIR scans using the SPM5 unified segmentation model (Ashburner and Friston, 2005). This step reduces the potentially confounding effect of scanner bias and renders the intensities of the FLAIR image more homogeneous.

Compared to the technique described by Focke et al., the implementation in this study had small modifications:

(1) Instead of using only the white matter voxel intensities in the anterior frontal white matter and pons as internal reference region, the white matter (WM) and gray matter (GM) of the whole brain were used as basis for intensity normalization.
(2) Instead of convolving the FLAIR scans with a Gaussian kernel, the spatially and intensity normalized FLAIR images were not smoothed but used directly as input for subsequent regional FLAIR analysis of the hippocampus (see below).
(3) Instead of applying the general linear model of SPM5 for statistical comparison with a control group, only descriptive statistics were used for this study (i.e. calculation of mean FLAIR intensities of right and left hippocampus; definition of a 95% confidence region for the hippocampal FLAIR intensities of the controls).

The following paragraphs describe the image processing in detail. It was based on standard procedures available within SPM5 (e.g., normalization, segmentation, etc.) and additional simple computations by the image calculation tool of SPM5 (e.g., multiplication of images, masking, etc.), and it was fully automated using a MATLAB® batch script. Starting point were a high-resolution T1 volume data set and a corresponding FLAIR image of the same patient which were transferred in digital imaging and communication (DICOM) format from the MR scanner to an AMD Opteron® 2.0 GHz PC and converted to ANALYZE format by means of the DICOM conversion tool of SPM5. For this study, the native T1-weighted volume data set of 1 mm^3 voxel resolution and the coronal FLAIR images