Morphometric analysis on T1-weighted MRI complements visual MRI review in focal cortical dysplasia

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ABSTRACT

Objective: Focal cortical dysplasia (FCD) is a common pathology in focal drug resistant epilepsy (DRE). Voxel based morphometric MRI analysis has been proposed as an adjunct to visual detection of FCD, which remains challenging given the subtle radiographic appearance of FCD. This study evaluates the diagnostic value of morphometric analysis program (MAP) in focal DRE with pathology-confirmed FCD.

Methods: Automated morphometric analysis program analysis generated z-score maps derived from T1 images, referenced to healthy adult or pediatric controls for each of 39 cases with pathology-confirmed FCD. MAP identified abnormal extension of gray matter into white matter (MAP-E) and blurring of the gray-white matter junction (MAP-J), independently of clinical data and other imaging modalities. MRI was visually reviewed by neuroradiologists as part of usual clinical care, and independently re-reviewed retrospectively by a neuroradiologist with > 10-years' experience in epilepsy MRI. Sensitivity and specificity were calculated for MRI, MAP, scalp-EEG, PET and SISCOM compared to resection area (RA).

Results: In this cohort of 39 histologically proven FCD cases, the sensitivity and specificity of MAP-J [64% (95% CI 48%–77%) and 96% (95% CI 93%–0.98%)] and MAP-E [74% (95% CI 59%–86%) and 94% (95% CI 91%–97%)] were higher than qualitative MRI review, SISCOM, and FDG-PET. Initial MRI review detected FCD in 17, expert review identified 26. Among cases not detected by initial MRI review, MAP-J correctly identified FCD in 12 additional cases and MAP-E in 13 cases. Among cases not detected by expert MRI review, MAP-J correctly identified 6 and MAP-E 8 cases. Excellent surgical outcome was achieved in 76% of patients.

Significance: MAP showed favorable sensitivity compared to visual inspection and other non-invasive imaging modalities. MAP complements non-invasive imaging evaluation for detection of FCD in focal DRE patients.

1. Introduction

Among patients with MRI-negative epilepsy, focal cortical dysplasia (FCD) is the most prevalent pathology (Wang et al., 2013). In current epilepsy surgery series, FCDs have been found to be the most common pathologic finding in pediatric patients, and the third most frequent lesion found in adult patients (Fauser et al., 2008; Hildebrandt et al., 2005; Tassi et al., 2002; Urbach et al., 2002). FCD is a type of malformation of cortical development, and is characterized by disrupted cortical lamination with or without dysmorphic neurons, balloon cells, and/or ectopic neurons in white matter (Blumcke et al., 2011; Tassi et al., 2002; Taylor et al., 1971), and constitutes a broad spectrum of histopathological and clinical features ranging from FCD type 1 (subtle lesions difficult to visualize with MRI) to FCD type 3 (severe pathology with other associated epileptogenic lesions) (Blumcke et al., 2011). Noninvasive (scalp) EEG findings can show regional polyspikes (Noachtar et al., 2008) but are otherwise similar to those found in patients with other types of epileptogenic lesions. The MRI features of

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FCD include changes in gyral size, abnormal gyral shape, decreased cortical T1 intensity, increased T2 signal, and poor gray and white matter differentiation (Colombo et al., 2009; Colombo et al., 2012; Leach et al., 2014). While some FCDs can be obvious on conventional neuroimaging, others can be quite subtle (Harvey et al., 2015). Clinical detection of FCD type II lesions by neuroradiologists has reported rates between 65% and 91% (Mellerio et al., 2014; Wagner et al., 2011).

To overcome some of the limitations of visual identification of FCDs with MRI, quantitative post-processing methods have been developed (Kassubek et al., 2002). Voxel-based morphometric analysis program (MAP) quantitatively assesses cortical anatomy and compares a patient's morphometric features with a group of healthy controls. The technique is a voxel-by-voxel quantitative comparison of gray-matter probability maps of individual patients with a mean grey-matter image from a normal database. This technique has been reported as a promising method in identification of malformations of cortical development such as FCDs and heterotopias (Huppertz et al., 2005; Huppertz et al., 2009; Kassubek et al., 2002; Wagner et al., 2011). MAP feature maps from T1 MPRAGE sequences in an adult cohort of nonlesional MRIs increased the detection of possible epileptogenic lesions when used in conjunction with conventional MRI, particularly in those cases with extratemporal localization (Doelken et al., 2012). The detection rate of subtle lesions by MAP in published series ranges between 43% and 85% (Huppertz et al., 2005; Wagner et al., 2011; Wang et al., 2014). A consideration for application of this technique in children, however, is the variability in brain maturation in pediatric subjects compared to adults. The clinical utility of MAP in young children should be considered carefully when using a normative database constructed from teenage and adult volunteers. The cortical thickness and myelination in younger differ from mature brains, and age-matched healthy controls would be a more appropriate comparison (Bruggemann et al., 2007).

In this study, we performed MAP in a cohort of consecutive histologically confirmed FCD cases. Review of MAP images was performed blinded to clinical details, seizure semiology, and information from scalp EEG, subtraction ictal SPECT coregistered to MRI (SISCOM), FDG-PET, and initial MRI review. Age-appropriate control datasets were used for pediatric and adult patients. The objective of this study was to determine the sensitivity and specificity of MAP analysis in a consecutive series of histopathologically-verified FCD cases and compare to other available presurgical modalities.

2. Methods

This is a retrospective non-interventional study approved by the Mayo Clinic Institutional Review Board at a National Association of Epilepsy Centers level 4 epilepsy center.

2.1. Patient selection

Adult and pediatric patients were retrospectively identified from consecutive patients at our institution who underwent resective surgery for epilepsy between 2001 and 2012 and had FCD confirmed by post-resection pathology. Fifty-seven patients were identified. Epilepsy patients younger than 5 years at time of surgery were excluded because healthy pediatric controls did not extend below this age group (14 patients). One patient was excluded due to lack of post-surgical follow-up. Three cases with extensive pathology and deformation, or previous lobar resective surgery were excluded from the analysis group, as these deformations caused artifacts in the post-processed MAP images. Thirty-nine cases, 19 pediatric (16 male, median 13 years, IQR 13-14) and 20 adults (8 male, median 37 years, IQR 32-42) with pathology confirmed FCD were available for the final analysis. FCD pathology was classified as type I, IIA, IIB, or III according to the International League Against Epilepsy 2010 classification (Blumcke et al., 2011). Indeterminate FCD included cases in which cortical dysplasia was the

pathology diagnosis but the report contained no description of dyslamination, dysplastic neurons, balloon cells, or associated pathology.

2.2. Normal controls

Adult and pediatric normal volunteers were recruited from the community and surveyed to exclude history of seizures, developmental delay, and headache. The adult control group was comprised of 64 adults (33 in the 18–45 age group, 17 male, median age 25.7 years;31 in 46–60 age group, 16 male, median age 44.7 years) after excluding five who could not complete imaging due to claustrophobia and five whose imaging showed incidental abnormal findings. Forty-one volunteers were scanned for the pediatric normative cohort. One subject with claustrophobia and four with incidental abnormalities found were excluded, resulting in a pediatric control group with twelve subjects in age group 5–9 years (7 male, median age 7.2 years), eleven in age groups 10–13 years (4 male, median age 11.3 years), and thirteen in age group 14–17 years (7 male, median age 16.3 years). The lower age limit was based on the assumption that 5-year-olds were the youngest age group able to cooperate with a non-sedated MRI, without significant motion artifact. The three pediatric groups were selected to account for the dynamic and variable brain maturation across childhood, early adolescence, and late adolescence (Lenroot and Giedd, 2006).

2.3. MRI acquisition

For control subjects and 10 epilepsy patients, a 3D fast gradient-recalled echo T1-weighted MPRAGE sequence was acquired on a 3.0 T scanner: Inversion Time (TI):/pulse repetition time (TR)/echo time (TE), 2300/7.5/3.1 milliseconds; 8 deg flip; matrix, $256 \times 256 \times 200$; field of view (FOV), 24.0×24.0 cm; slice thickness, 1.0 mm; bandwidth, ± 31.25 kHz; and 1 excitation signal acquired. The early patients in the cohort (N = 29) had a 1.5 T SPGR (TR = 23, TE = 10, 25 deg flip, 256×256 matrix, 22.0×22.0 cm FOV; 1.6 mm slice thickness, 1 excitation signal acquired) T1 weighted sequence.

2.4. Image processing methods

The MAP image processing methods were implemented in SPM-12 (Friston et al., 2007) under Matlab (Mathworks Inc., Natick MA), paralleling the previously described SPM-5 implementation (Huppertz et al., 2005; Huppertz et al., 2009). The MAP methods operated on a T1-weighted structural MRI, and produced two derived images: the extension (identifying abnormal extension of cortical gray matter) and junction (showing abnormal thickening or blurring of the gray matter [GM] and white matter [WM] junction) (Huppertz et al., 2009; Wagner et al., 2011). The T1-weighted image was first recentered manually on the anterior commissure, and large deviations from a standard orientation were corrected to ensure consistency. The MRI was non-linearly registered to the SPM-12 atlas space (IXI tissue probability map, http://brain-development.org) (Brett et al., 2001).The image volume was grayscale bias corrected and segmented into probabilistic masks for gray matter, white matter, cerebrospinal fluid, and extra-cerebral tissues using both spatial location in atlas space and voxel intensity (Ashburner and Friston, 2005). To create the extension image, the gray matter mask was blurred by smoothing with a 6 mm isotropic Gaussian kernel. On a voxel-wise basis, the mean of the blurred GM masks of the normal controls was subtracted from the patient's blurred GM mask, and the result was divided by the standard deviation of the normal controls creating a z-score map. This map was transformed into patient space using the inverse of the original transform to atlas space, creating the final extension image.

The junction image was similarly generated from the segmented brain tissue masks in atlas space. The GM and WM masks were used to compute the mean and standard deviation of GM and WM pixel intensities in the T1 weighted image in atlas space. A mask of the GM-WM