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Novel surface features for automated detection of focal cortical dysplasias in paediatric epilepsy

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ABSTRACT

Focal cortical dysplasia is a congenital abnormality of cortical development and the leading cause of surgically remediable drug-resistant epilepsy in children. Post-surgical outcome is improved by presurgical lesion detection on structural MRI. Automated computational techniques have improved detection of focal cortical dysplasias in adults but have not yet been effective when applied to developing brains. There is therefore a need to develop reliable and sensitive methods to address the particular challenges of a paediatric cohort.

We developed a classifier using surface-based features to identify focal abnormalities of cortical development in a paediatric cohort. In addition to established measures, such as cortical thickness, grey-white matter blurring, FLAIR signal intensity, sulcal depth and curvature, our novel features included complementary metrics of surface morphology such as local cortical deformation as well as post-processing methods such as the "doughnut" method - which quantifies local variability in cortical morphometry/MRI signal intensity, and per-vertex interhemispheric asymmetry. A neural network classifier was trained using data from 22 patients with focal epilepsy (mean age = 12.1 ± 3.9, 9 females), after intra- and inter-subject normalisation using a population of 28 healthy controls (mean age = 14.6 ± 3.1, 11 females). Leave-one-out cross-validation was used to quantify classifier sensitivity using established features and the combination of established and novel features.

Focal cortical dysplasias in our paediatric cohort were correctly identified with a higher sensitivity (73%) when novel features, based on our approach for detecting local cortical changes, were included, when compared to the sensitivity using only established features (59%). These methods may be applicable to aiding identification of subtle lesions in medication-resistant paediatric epilepsy as well as to the structural analysis of both healthy and abnormal cortical development.

1. Introduction

Focal cortical dysplasias (FCDs) are the most common cause of surgically remediable drug-resistant epilepsy in children (Lerner et al., 2009). Surgical resection can result in reduced need for anti-epileptic medication, reduced frequency or most commonly complete absence of seizures (Cross, 2002; D'Argenzio et al., 2011, 2012) There is evidence too that it can even improve developmental outcome (Skirrow et al., 2011, 2015). The challenge in many cases is to accurately locate the area of responsible tissue. Surgical outcome is significantly improved when lesions are identified on MRI scans pre-surgically (Téllez-Zenteno et al., 2010). However between 50 and 80% of FCDs are too subtle to detect by conventional radiological analysis of MRI scans (Besson et al., 2008). While progress has been made in improving the detection of FCDs in adults using structural neuroimaging techniques (Thesen et al., 2011; Wang et al., 2015) and automated classifiers (Ahmed et al., 2015; Hong et al., 2014), automated lesion classification has not been attempted in a solely paediatric cohort despite this being a congenital condition (Chen et al., 2014). Therefore an automated tool capable of improving the detection of FCD in the paediatric population would represent an important step in improving the quality and consistency of presurgical evaluation with implications for surgical outcome.

Applying automated lesion detection methods in a paediatric population raises a number of unique challenges. First, between the ages of one and 18 the cortex undergoes major structural changes including

Abbreviations: AUC, area under the curve; FCD, focal cortical dysplasia; FLAIR, fluid-attenuated inversion recovery; LCD, local cortical deformation; LGI, local gyrification index; PCA, principal component analysis; ROC, receiver operator characteristic.

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cortical thickening and thinning (Giedd et al., 2015; Gogtay et al., 2004; Raznahan et al., 2011; Shaw et al., 2008), as well as changes in gyrification (Li et al., 2014) and myelination (Deoni et al., 2015; Whitaker et al., 2016a, 2016b), thus identifying focal abnormalities in cortical structure requires careful consideration of developmental trajectories. For example, an apparent thickening of cortex may not necessarily signify an abnormality for a given individual at a given age. Second, motion artefacts are more prevalent in paediatric imaging affecting the accuracy of established surface-based features (Ducharme et al., 2015). Sensitivity to detect FCDs may therefore be improved by novel features and post processing methods measuring different aspects of cortical structure.

FCDs include a spectrum of localized malformations of cortical development, manifesting as an array of characteristic radiological features. One classification system developed by the International League Against Epilepsy (ILAE) (Blümcke et al., 2010) defines histological subtypes as follows. FCD type I have abnormal radial and tangential lamination; FCD type II are associated with aberrant cytology, such as large dysmorphic neurons plus/minus balloon cells; and FCD type III occurs with another lesion, e.g. hippocampal sclerosis. Radiologically, FCDs have been associated, albeit inconsistently, with a range of features including local cortical thinning or thickening, blurring of the grey-white matter boundary, abnormal cortical folding patterns, increased signal intensity on FLAIR/T2-weighted MRI (including the transmantle sign in FCD Type IIB) and interhemispheric asymmetry in any of the above traits (Colombo et al., 2003, 2012; Yagishita et al., 1997). The variable presentation of these radiological features and the fact that they are often small and subtle, means that they are easily missed on visual inspection by radiologists (Wagner et al., 2011).

To overcome the difficulty of radiological assessment of FCDs, automatic detection methods build a series of morphological measures into an identification algorithm to improve detection rate (Ahmed et al., 2015; Besson et al., 2008; Hong et al., 2014; Thesen et al., 2011). For example, surface-based techniques may be used to calculate various measures such as cortical thickness (Fischl and Dale, 2000), signal intensity in the grey or white matter (Salat et al., 2009), local gyrification index (LGI) (Schaer et al., 2008), sulcal depth and curvature (Fischl et al., 2004) at each point on the cortical surface (henceforth vertices). These measures provide an improved detection rate, with rates as high as 74% in adult cohorts (Hong et al., 2014), compared to other approaches such as diffusion tensor imaging (DTI), voxel-based morphometry (VBM), (see reviews: (Bernasconi et al., 2011; Martin et al., 2015)). However automated classification using surface-based measures has not been applied to a paediatric cohort, and, owing to the particular differences between adult and paediatric brains it is unclear that current approaches are suitable or would yield similar results.

Our overall approach to develop a tool for automated FCD detection, which addresses the particular challenges of a paediatric cohort, was to optimize the ability to find and quantify each area of cortex in terms of how it differed from healthy cortex. To this end, we calculated structural measures and applied post-processing methods to quantify a number of radiological identifiers of focal cortical dysplasias. First, established structural markers of FCD - cortical thickness, intensity contrast at the grey-white matter boundary and FLAIR signal intensity - have normal developmental and regional differences which can obscure locally abnormal values within an FCD. To address this we normalised measures within subjects, calculated interhemispheric asymmetries of these measures and normalised the values for each vertex relative to a group of healthy paediatric controls. Moreover, FCDs are characterised by focal changes in these structural markers and thus subtle lesions should be identifiable as local areas of abnormal cortical thickness, grey-white matter contrast and FLAIR signal intensities. We quantified these local changes by creating a "doughnut" method, which calculates the difference between an area of cortex and its surrounding annulus at each vertex, highlighting where these differences are greatest. Finally noise and particularly motion artefacts are common problems in paediatric scans. Intrinsic curvature, a small scale measure of cortical shape deformation, only requires an accurate pial surface and is unaffected by motion-related inaccuracies in the segmentation of the grey-white matter boundary. Furthermore, it is more sensitive to subtle cortical abnormalities than larger scale folding parameters measures such as LGI (Ronan et al., 2014). We therefore developed a measure of local cortical deformation (LCD) based on the magnitude of intrinsic curvature surrounding each vertex (Ronan et al., 2011), as a more robust measure of cortical shape. The added value of these structural markers and post-processing methods – local cortical deformation, interhemispheric asymmetry and the "doughnuts" of structural measures - were then combined with the established surface-based metrics for FCD detection (cortical thickness, grey-white matter intensity contrast, FLAIR signal intensity, curvature and sulcal depth) in a neural network trained to classify cortical regions into lesional and nonlesional vertices. Furthermore we directly compared our measure of cortical shape, LCD, with the existing measure LGI.

2. Materials and methods

2.1. Participants

A retrospective cohort of 27 patients with radiologically defined FCD (mean age = 11.57 ± 3.96, range = 3.79–16.21 years, 10 females) who underwent 3D T1 and FLAIR imaging on the 1.5T MRI scanner at Great Ormond Street Hospital as part of their clinical workup were studied, following permission by the hospital ethical review board. Cases were identified by searching the medical reports for a radiological diagnosis of FCD. Exclusion criteria were patients scanned using a different MRI scanner or protocol. The following information from the medical notes was gathered for all patients included in this study: age at epilepsy onset, duration of epilepsy, radiological report, current anticonvulsant medications and, where applicable, post-surgical histology. A control group of 28 term-born children with no history of any neurological diagnosis (mean age = 14.57 ± 3.06, range = 10.1–19.75 years, 11 females) were recruited by advertisement.

2.2. MR imaging

All participants were scanned on a 1.5T Avanto MRI scanner (Siemens, Elangen, Germany). Three-dimensional data sets were acquired using a T_1-weighted 3D-FLASH sequence (TR = 11 ms, TE = 4.94 ms, FOV = 256 × 256 mm, flip angle = 15°, voxel size = 1 × 1×1 mm^3) and T_2-weighted FLAIR sequence (TR = 6000 ms, TE = 353 ms, TI = 2200 ms, FOV = 256 × 256 mm, flip angle = 15°, voxel size = 1 × 1 × 1 mm^3). Anonymised FLAIR and T1 volumetric scans were rated from one to five according to severity of motion artefact. The following classification system was used: 1) no visible motion artefacts, 2) subtle artefacts visible, 3) mild ringing artefacts, 4) severe ringing artefacts and 5) adjacent gyri indistinguishable due to motion.

2.3. Cortical reconstruction

FreeSurfer software v5.3 (Dale, 1999; Fischl and Dale, 2000; Fischl et al., 1999) was used to generate the cortical reconstructions and to co-register the FLAIR scans to T1-weighted images. In outline, *FreeSurfer* firstly sub-samples the raw image data voxels to 1mm^3 isotropic voxels. The data is then normalised for intensity and RF-bias field inhomogeneities are modeled and removed. The skull is then removed from all of the images using a skull-stripping algorithm (Ségonne et al., 2004). Subsequently, cerebral white matter is identified, and the hemispheres are separated, tessellated and deformed to create accurate smooth mesh representations of the grey-white matter interface and pial surface, with approximately 150,000 vertices per hemisphere. Within-subject registration of FLAIR scans to T1 images was performed using a boundary-based cost function; the white-matter boundary is mapped to the FLAIR image and the FLAIR intensity is sampled per-vertex either side