An automatic classificator based on local fractal features for the identification of cortical malformations

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TARGET AUDIENCE – Scientist and clinicians with interest in automatic detection and quantitative characterization of cortical malformations

PURPOSE: Malformations of cortical development (MCDs) encompass a wide spectrum of brain abnormalities whose extension and localization are extremely variable from subject to subject. MRI is a non-invasive method allowing the in-vivo evaluation of cerebral cortex geometry. Quantitative analysis of the cortex is generally performed using well-known methods[1,2], but these may fail when applied to patients with large architectural deformations. Moreover they rely on the analysis of groups of subjects, that is not suitable for the single-subject diagnosis we are interested in, or on features as cortical thickness, which are not always altered in MCDs. This study presents a powerful diagnostic tool able to provide the clinicians with a quantitative characterization of each malformation.

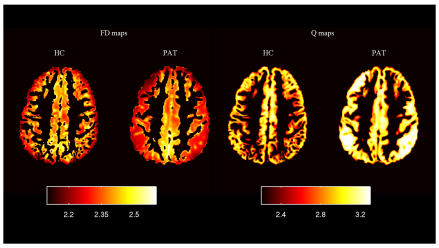

Figure 1 Example of FD and Q maps for a healthy subjects and a patient with cortical malformations. Notice lower FD values and higher Q values in the malformed areas respect to the HC.

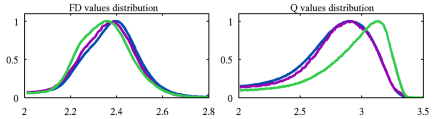

Figure 2 FD and Q distributions for HC (blue line) and MCD patient healthy (violet line) and pathologic (green line) tissues., HC and healthy tissue of MCDs are similar, while pathologic tissue assumes lower FD. The difference is even clearer in the Q distribution.

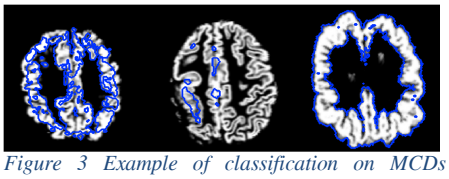

Figure 3 Example of classification on MCDs subjects (malformations in blue) In blue the areas classified as pathological.

DATA: 19 healthy controls (12 males, 7 females, mean age and SD 9.65 ± 2.46 yrs) and 9 patients affected by MCDs (3 males, 6 females, mean age and SD 7.82 ± 2.33 yrs) underwent a MRI scan with a 3T Philips scanner. For each subject a 3D T1-weighted sequence was acquired (TE=3.5ms; TR=8ms; flip angle=8°; voxel size 1x1x1mm^3).

METHODS: We developed an analysis framework based on fractal geometry. We extended the original box-count algorithm[3], that provides a global fractal dimension (FD). i.e. a value for each object (brain), to compute a local FD value, i.e. a value for each voxel *V(x,y,z),* thus creating a 3D map of FD. More precisely, we counted the number of boxes needed to cover the neighborhood of V increasing its size up to r_{max} (r_{max} should be greater than the expected lesion size, in our case we set it to 40 voxels) and computing the FD with a regression analysis. Then, the FD value is assigned to the voxel V. We also computed the constant of the linear regression (Q) obtaining a second map. *Figure 1* reports two examples of voxel based maps of a healthy control (HC) and of a patient (PAT). Subsequently, the control population was divided into a training set and a testing set, with the latter including also all patients.

A study specific template of the gray matter (GM)[4] was built on the training set to perform voxelwise analysis, and FD and Q maps for both the training and the test sets were warped to the template space. We computed the normalized FD histogram for each subject (*S)* and used the training set to build a reference histogram h_{HC}. Then, we defined the histogram distance map for the FD histogram of the test-set subjects as $P_h(V,S) = |h_S(FD(V)) - h_{HC}(FD(V))|$.

We modeled the FD distribution around V with a Gaussian function and computed its mean and SD (μ_{HC}, σ_{HC} for the reference subjects, μ_S, σ_S for the subjects in the test-set). Then, we defined the local distribution distance (P_l) as: $P_l(FD,S,V) = \left|\mathrm{Norm}\left(FD_S, \mu_{FD,S}, \sigma_{FD,S}\right) - \mathrm{Norm}\left(FD_S, \mu_{FD,HC}, \sigma_{FD,HC}\right)\right|$. Finally, we classified the voxel V as healthy or pathologic using the following classifier:

$\Psi(\mathrm{FD},\mathrm{S}) = P_h(FD,S)P_l(FD,S) \geq \chi_l \ \cup (P_h(FD,S) \geq \chi_h)$ where χ_l and χ_h are the tunable parameters of the algorithm. The entire analysis was repeated for the Q maps. An experienced neuro-radiologist drawn for each subjects ROIs including either healthy or pathologic tissues, which were used for the parameter tuning and the performance assessment.

RESULTS: HCs and PATs show a significant difference of both FD (2.416±0.007 for the HCs, 2.386 ± 0.019 for PATs, p=1.44E-5) and Q (2.386±0.019 for the HCs, 2.827±0.059 for PATs, p=9.21E-5). The distributions of the fractal indices in the different tissues are reported in *Figure 2*. For the evaluation of the classification algorithm, we set χ_h and χ_l in order to maximize the accuracy and to minimize the false positive rate (FPR), respectively. Detailed performances of the classificatory are reported in Table 1. An example classification on three subjects is presented *Figure 3*, where the blue lines delimit the areas classified as pathological.

DISCUSSION: The fractal dimension proved to be able to characterize the geometrical properties of the cortex. Patients with MCDs have statistically different FD and Q values respect to normal subjects as expected from histology and literature, with lower average FD values. We attributed the right shifting of MCD Q histograms to a thicker or more densely packed cortical layer as the number of non-zero voxels in the neighborhood directly influences Q, while the FD histograms point out the complexity reduction in pathological brains. We also proved that the distributions of fractal values are tissue specific and able to differentiate healthy tissue in pathological subjects from malformed areas (*Figure 2*). Visual inspection of the areas classified as pathological shown that while histogram distance maps classified the majority of diffuse pathologies, the local distance were essential for the correct classification of focal lesions, as the one visible in the middle of *Figure 3*.

Performances	
Accuracy (Weighted)	0.81 (0.82)
Specificity	0.80
Sensitivity	0.84
Precision	0.57
AUC	0.89

Table 1 Synthetic performances for the threshold that maximizes accuracy.

CONCLUSION: We proved that fractal indices are able to reveal the MCDs and to distinguish the healthy and pathologic brain tissues. The voxel-based box-count and the local distance maps allowed the correct classification of MCDs, even for the focal ones. Our method provides high accuracy, and setting the parameters of the algorithm it is possible to handle the specificity/sensibility of the classifier. From a clinical point of view our method only needs a T1w scan, does not need user interaction, can be automatically applied on large datasets and tuning the threshold it is possible to enhance malformation detection when necessary.

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