Spatial Heterogeneity Analysis of Brain Activation in Epilepsy

Lalit Gupta[1], René M.H. Besseling[2,3], Geke M. Overvliet[2,4], Paul A.M. Hofman[2,4], Anton de Louw[2], Maarten Vaessen[2,3], Albert P. Aldenkamp[2,4], Shrutin Ulman[1], Jacobus F.A. Jansen[3,4], and Walter H. Backes[3,4]

[1]Philips Electronics India Ltd., India, [2]Epilepsy center Kempenhaeghe, Heeze, Netherlands, [3]Research School for Mental Health & Neuroscience, Maastricht University, Netherlands, [4]Maastricht University Medical Center, Maastricht University, Netherlands

Target Audience

Researchers working in the area of the clinical applications of functional Magnetic Resonance Imaging (fMRI) of the brain.

Purpose

In many brain diseases it has been observed that spatial patterns in blood oxygenation level dependent (BOLD) activation maps appear more (diffusively) distributed than in healthy control brains. However, measures that can quantitatively characterize this spatial distributiveness in individual subjects are currently lacking. In this study, we have evaluated the spatial heterogeneity[1] of brain activation maps by applying a number of conceptually different measures. These measures were tested on functional MRI language activation maps of children with Rolandic epilepsy with impaired language skills and were compared to age-matched healthy controls.

Method

The proposed heterogeneity analyses focus on different aspects of spatial heterogeneity of binarized activation maps. The different methods are sensitive to shape (isoperimetric quotient), configuration (co-occurrence matrix derived entropy and homogeneity and fractal dimension[2]) and sparsity (lacunarity[2]) of the activation patterns. Figure 1 shows a conceptual set of 2D model images to illustrate variations of the various spatial heterogeneity measures.

Twenty-three children (age 8-14 years) with Rolandic epilepsy were selected based on electrophysiologic criteria and seizure semiology, associated language impairment was confirmed using neuropsychological testing (Clinical Evaluation of Language Fundamentals, 4th edition). Using a standard task block design (30s task and rest blocks, repetition time 2s, 3 Tesla), Subjects had to covertly generate as many words as possible starting with a visually presented letter (U-N-K-A-E-P)[3] Activation maps were calculated and compared between groups using SPM (Welcome Department of Cognitive Neurology, London, UK).

We determined the heterogeneity measures of the activation maps for each individual subject. Subsequently, patients and controls were statistically compared for each heterogeneity measure. The F-score was calculated for each heterogeneity measure by the ratio of inter-class variance (discrimination between patients and controls) and intra-class variance (variance within patients and controls). The higher the F-score is, the more likely this feature is highly discriminative for distinguishing patients and controls. Each heterogeneity measure was analyzed as a function of threshold x % (x range: 3-10) most significantly activated voxels. To investigate the dependency of the various heterogeneity measures, for each pair of measures, Pearson's correlation coefficient was calculated.

Results

No activation map group differences were found between patients and controls using standard fixed effects SPM analyses. Heterogeneity measures are listed in table 1. The number of activated regions, fractal dimension, entropy and homogeneity indicated slightly, but not significantly, increased heterogeneity for patients relative to controls. Shape and sparsity provided significantly higher heterogeneity values for patients than controls; these two measures also showed high F-scores. All the measures, other than the number of activated regions, showed that the difference between patients and controls remained more or less constant as a function of activation threshold. Figure 2 shows this trend for the shape (isoperimetric quotient) and sparsity (lacunarity) measures. The correlation between the measures is listed in table 2. All measures, other than number of activation regions, show moderate to high correlation (0.7 to 0.9).

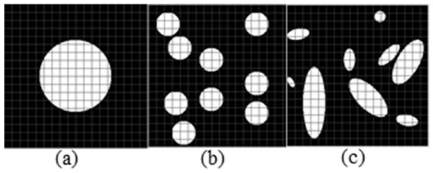

Image	(a)	(b)	(c)
No. of reg.	1	9	9
Fractal	1.98	2.65	2.46
Isoperim.	0.70	0.08	0.09
Entropy	1.31	1.75	1.69
Homog.	3094	2829	2906
Lacunarity	2.11	11.40	18.96

Figure 1: Illustration of spatial heterogeneity in a set of model images (a)-(c) in which the objects (surrogate activation regions) vary in size, shape and organization. The number of object pixels was kept constant. The table shows the variation in heterogeneity values. Note that isoperimetric quotient and lacunarity provide the strongest variations.

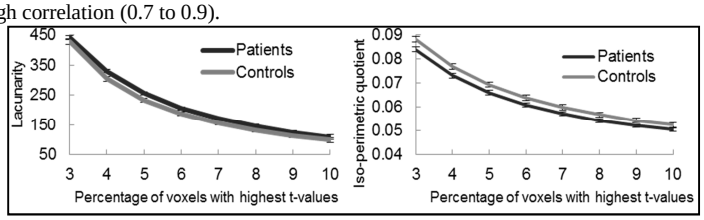

Figure 2: Lacunarity and isoperimetric quotient in patients and controls as a function of the percentage most strongly activated voxels. Both heterogeneity measures increase when less voxels are selected as the number of isolated voxels decreases.

Discussion

All proposed measures of spatial heterogeneity revealed that patients exhibit a more heterogeneous language activation pattern than controls. Heterogeneity of activation maps cannot be described by a single measure, as the various measures appear moderately correlated. The two most important discriminating features were shape (isoperimetric quotient) and sparsity (lacunarity). An interpretation of increased spatial heterogeneity in brain disease is that additional brain regions may co-activate to compensate for or add to the disturbances in specific functional networks[4]. Such a compensation mechanism creates more irregular and smaller regions in the activation maps and also spatially disperses regions. We propose that spatial heterogeneity is a potentially valuable functional biomarker that could be added to regular brain activation analysis to characterize conditions of cerebral disease, in particular when no differences in group activation maps are found.

Table 1: Heterogeneity measures and F-score in patients and healthy controls.

Method	Patients	Controls	p-value	F-score
No. of activated regions	51.1± 2.2	49.3± 3.1	0.47	0.04
Fractal Dimension	3.15± 0.01	3.14± 0.01	0.33	0.26
Isoperimetric quotient	0.0659 ± 0.001	0.0694± 0.001	0.01	0.33
Entropy	1.89±0.02	1.83±0.02	0.09	0.20
Homogeneity	21128±80	21281±81	0.09	0.19
Lacunarity	256.3±5.8	233.3±6.8	0.01	0.41

Notation: mean ± standard error

Table 2: Matrix with correlation between different measures.

	Fractal	Shape	Entropy	Homog.	Lacunarity
No. of reg.	0.04	-0.15	0.09	-0.05	0.05
Fractal		-0.73	0.85	-0.86	0.67
Shape			-0.78	0.77	-0.83
Entropy				-0.88	0.68
Homog.					-0.69

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References

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