Robust Assessment of Cortical Thinning in Brain MRI by Generalized Complexity Measures

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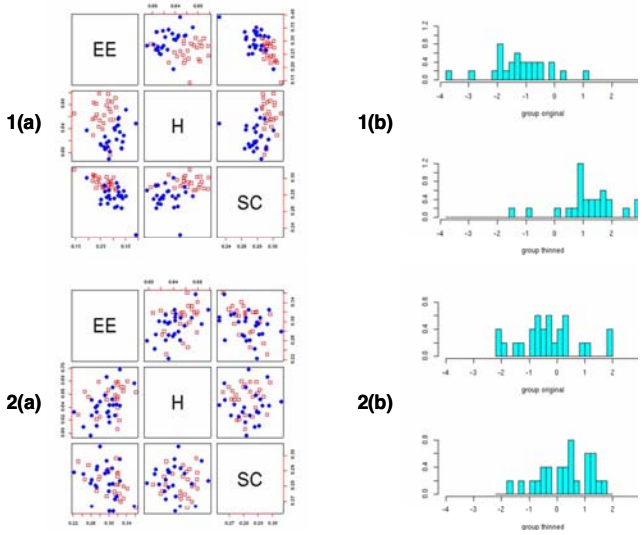
INTRODUCTION: Recent brain MRI studies of aging and dementia have suggested methods for precise measurement of patterns of cortical thinning [1]. These methods, though yielding promising results, depend on a number of parameters for smoothing, mapping the cortical surface, and choosing a thickness metric [1]. This study presents a robust method for detecting cortical thinning that requires minimal intervention and is applicable to the study of arbitrary brain regions and image modalities. It utilizes information theoretic quantities introduced in [2] and generalized in [3], obtained directly from segmented images, in particular: 1) entropy (*H*), which quantifies the multiplicity of patterns in the segmented image(s), 2) statistical complexity (*SC*), which quantifies the correlation structure of the patterns, and is quantitatively the average *information* for observation of a pattern, conditioned on the observation of an adjacent pattern, and 3) excess entropy (*EE*), which quantifies the convergence of the pattern distribution as a function of scale. The main objective was to test detection of minimal changes in brain structure, such as cortical thinning.

	MANOVA *p*	LDA *p*	SENS.	SPEC.
WB	0.1953	0.0288	0.59	0.52
TL	0.0023	0.0002	0.73	0.63
STG	6.59e-06	1.74e-07	0.80	0.76
LSTG	0.2043	0.0304	0.60	0.55
RSTG	4.1e-09	5.67e-11	0.91	0.85

METHODS: The methods are demonstrated using a data set introduced in [1], a set of 50 segmented T1 MRI images from the ICBM data set [4], 25 of which had the cortical surface in the right superior temporal gyrus (RSTG) artificially thinned by an average of 0.5 mm, originally generated to study various cortical thickness measurements. Use of this data set demonstrated the robustness of the techniques to normal population variations in brain structure. The first step in the analysis is the generation of a histogram for all length *L* sequences in a region where the symbols in the sequence represent the segmented values (e.g. gray matter, white matter, and CSF in the current study). Since the image resolution was 1 mm and average thinning was 0.5 mm a minimal sequence length of 2 mm was chosen for histogram generation. Calculation of *EE* requires an extrapolation to length 0 from longer lengths so histograms of length up to 12 mm were also generated. The methods for calculating *H*, *SC*, and *EE* from the histograms are described in [3]. The calculations were done for successively refined regions of: whole brain (WB), temporal lobe (TL), superior temporal gyrus (STG), and right and left superior temporal gyrus (RSTG, LSTG). The regions were masked using a somewhat crude (2 mm resolution) labeled version of the MNI atlas [5] superimposed on the images (1 mm resolution). In addition, to normalize for population variations in brain structure, *H* and *SC* for each region were divided by the equivalent 12 mm quantity from the whole brain analysis and, as *EE* effectively uses values over all scales within a region it was divided by a measure of tissue asymmetry in the region for each subject. To asses the significance for separating the groups (thinned and not thinned from the original group), Wilks lambda for a MANOVA on *H*, *SC*, and *EE* was used. To test use of the combined complexity measures a linear discriminant analysis (LDA), and Welch two sample t-test on the resulting first linear discriminant were performed. The sensitivity and specificity were assessed using 10 times 10-fold cross validation on the LDA results.

RESULTS: As expected the ability to separate the group with cortical thinning in the RSTG from the group with no thinning increased as the complexity calculations were progressively constrained from WB to a region approximately encompassing the RSTG. Also as expected, the analysis on the LSTG, the only region containing no thinning, produced no separation in the groups (RSTG and LSTG results in Figure 1). The significance test results are summarized in the table. Already at the level of the temporal lobe some ability to separate the groups is apparent and the results are highly significant at the level of the superior temporal gyrus and right superior temporal gyrus. Even using maximally conservative Bonferoni multiple comparisons corrections for all labeled brain regions, the results for the RSTG are significant by more than 4 orders of magnitude. Though this was a relatively small data set, the sensitivity and specificity measures indicate that the complexity measures could provide great clinical utility. The figure shows scatterplots and histograms for the RSTG and LSTG analyses respectively. Figure 1(a) shows the values of *H*, *SC*, and *EE* in the RSTG for all 50 subjects, those for which the cortex was thinned represented by the open squares. Figure 1 (b) shows a histogram of the values for the 2 groups projected onto the first linear discriminant and indicates the separation between the groups. Figures 2 (a) and (b) show the same plots for the LSTG analysis.

Figure 1



DISCUSSION AND CONCLUSIONS: The complexity measures employed in this study proved highly sensitive at detecting very slight, focal changes in cortical thinning. As opposed to other detection methods, virtually no parameter tuning (save a choice of scale) was required. Though these measures are capable of detecting quite subtle effects the reason for their effectiveness in the current study is straightforward. The joint pattern histograms are dominated by homogenous regions of gray and white matter, with an imbalance toward gray matter for the RSTG. Thinning the cortex renders the histograms more uniform, which increases both the entropy and the complexity and accounts for the larger correlations in these measures than is typically observed. On the other hand, the separation of the two groups was not perfect which could be due to the complexity measures capturing cortical features other than thinning, such as surface area and curvature that did not vary between groups. In conclusion, the generalized complexity measures appear to provide quantitative and robust assessments of brain alterations in neurodegenerative diseases.

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