Towards an Imaging-Metric for Pre-Symptomatic Manifestations of ALS

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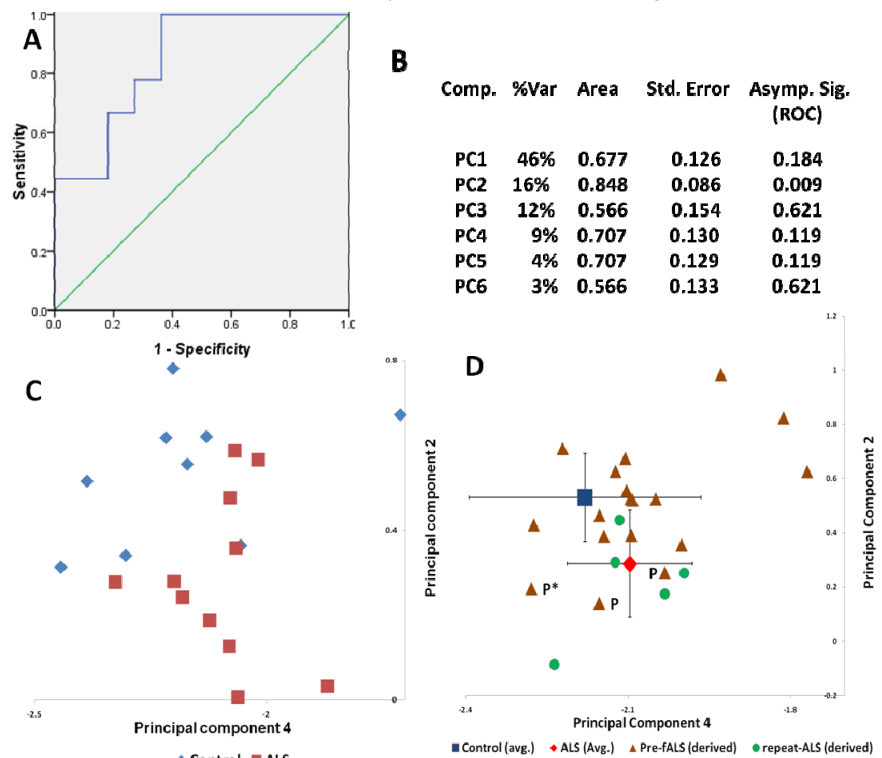
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Introduction: DTI and T_1-weighted MRI have been well documented to detect changes associated with amyotrophic lateral sclerosis (ALS), a neurodegenerative disease affecting the motor neurons. We hypothesize that a metric derived from a combination of these MRI parameters from the cortico-spinal tract (CST) and motor cortex could be a good indicator of the disease state. Such a metric may not only be of great prognostic value, but also may be sensitive enough to detect disease manifestations in pre-symptomatic subjects. To this end, we developed a metric using principal component analysis (PCA) on MRI parameters and tested it with repeat-scans on ALS as well as on pre-symptomatic subjects recruited from a study of individuals predisposed to developing a familial form of ALS (Pre-fALS) due to mutations in copper-zinc superoxide dismutase (*SOD1*) gene.

Method: Eleven patients clinically diagnosed with ALS (4 female, age=46 ± 11 years, median disease duration=343 days, ALS functional rating score (FRS-R)=38 ± 6), 9 age-matched healthy control subjects (6 females, age=45 ± 14 years) and 18 Pre-fALS (15 female, age=44 ± 12 years) were scanned on a Siemens 3T Tim system. MRI was also repeated in 5 ALS subjects (repeat-ALS scans, 1 female, age=47 ± 12 years, median duration=286 days, ALSFRS-R=41 ± 4, median time between scans=60 days). Standard DTI (Double spin echo EPI, 2 mm isotropic resolution, 2 averages) and T_1-weighted images (MPRAGE, TI=900 ms, 1 mm isotropic resolution, 1 average) were acquired in the brain, and DTI (Double spin echo EPI, 1.25x1.25x2.5 mm^3 resolution, 4 averages) was acquired in the cervical cord of all subjects. DWIs were corrected for susceptibility distortions (NeuroImage 20:870) and DTI reconstructed using FSL (Analysis Group, FMRIB, Oxford, UK). After co-registration, ROIs were drawn in the internal capsule, cerebral peduncles, and the white matter in the pons, pyramids, and cervical cord segments (C1-2 to C6) based on atlas or B0 images. Average FA, RD, MD and AD from these ROIs were determined for each subject. Signal intensities from T_1-weighted images were modulated with Jacobian of the warp field to account for volumetric changes (FSL) and modulated signal intensities from ROIs drawn on premotor cortex, primary motor cortex, and regions along the WM in CST were determined for each subject. Eighty-six parameters so-derived from 11 ALS and 9 control subjects served as the input for PCA, and the weights for the first 6 principal components (PCs) extracted to derive the PCs for 5 repeat-ALS scans as well as all Pre-fALS subjects. ROC analysis was done for each PC, and scatter plots between PCs generated for each group of subjects.

Comp.	%Var	Area	Std. Error	Asymp. Sig. (ROC)
PC1	46%	0.677	0.126	0.184
PC2	16%	0.848	0.086	0.009
PC3	12%	0.566	0.154	0.621
PC4	9%	0.707	0.130	0.119
PC5	4%	0.707	0.129	0.119
PC6	3%	0.566	0.133	0.621

Results: PC 2 accounted for 16% of the variability in the data and was significantly different between the ALS and control subjects (p=0.007), while PC1 and PC5 accounted for 47% and 4% variability and approached significance at p=0.289 and 0.134 respectively. ROC analysis performed on PCs from 11 ALS and 9 control subjects gave the largest area under the curve for PC2 (Fig. A blue line, area under curve=0.848, p=0.009), followed by PC4 and PC5 (Table B). The ALS and control subjects were moderately-separable in a scatter plot between PC4 and PC2 (Fig. C). When PCs derived from the repeat-ALS were added to the ROC analysis, the AUC for PC2 improved to 0.875 (p=0.002) and for PC4 improved to 0.715 (p=0.079). A scatter plot between derived PC2 and PC4 for repeat-ALS (Fig. D, green circle) and Pre-fALS (brown triangles) shows all 5 repeat-ALS and 8 Pre-fALS had PC2 less than mean+standard deviation of the ALS group. Furthermore, PC2 from 3 Pre-fALS were below the average-PC2 of ALS group (labeled P), one of whom clinically progressed to ALS (labeled P*) 12 months after the MRI scan. Clinical statuses of the other 2 Pre-fALS subjects were not changed at 6 and 7 months since their MRI scan, and they are being actively followed-up by clinical and MRI evaluations.

Discussion: While the SOD1 mutations in Pre-fALS subjects predispose them for ALS, there are no biomarkers to track their progression even though the disease process is believed to start before any physical manifestation of symptoms. DTI and T_1-weighted images are sensitive to neurodegenerative process, and our results suggest that parameters derived from MRI in the CST and motor cortices could potentially be combined into a metric to predict the disease state in repeat test on ALS patients as well as the pre-symptomatic individual who progressed to manifest ALS. However, additional longitudinal evaluations of the other 7 Pre-fALS subjects are required to fully evaluate specificity of this model. Furthermore, PCA is only one analytical method that can potentially be used to derive an imaging metric; other techniques such as logistic regression models are also being explored.

Conclusion: PC2 derived from T1 and DTI in the brain and DTI in the cord was a reasonable predictor of disease state in the ALS and Pre-fALS subjects tested. Further longitudinal and cross-sectional studies are underway to validate the metric derived here. A metric such as the one developed herein could one day form the basis for an imaging-biomarker of disease progression in ALS.