High-Resolution Longitudinal Voxel-Based Morphometric Study in ALS

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Introduction:

Amyotrophic lateral sclerosis (ALS) is usually a rapidly progressing neurodegenerative disease that destroys the upper and lower motor neurons responsible for voluntary muscle control. Despite the usual rapid progression of ALS, few longitudinal voxel-based morphometry (VBM) studies of ALS have been performed [1]. In this longitudinal ALS study, high-resolution VBM was performed using RAVENS [2-5] for GM, white matter (WM), and ventricles (VENT) at baseline, 6 months, and 12 months.

Method:

Fourteen ALS subjects (10 male and 4 female, average age 56.3±13.3 years) and 14 age and gender matched normal control subjects (average age 56.0±13.0, p=0.76) received a whole brain T_1-weighted MDEFT (TE=3.14 ms, TR=10.55 ms, TI=680 ms, SENSE factor=2, 20° flip angle) scan on a Philips Intera 3.0 T system with isotropic 1mm voxel size. Eight ALS subjects returned for a second scan approximately 6 months after baseline and 5 subjects at approximately 12 months. Images were segmented into GM, WM, and cerebrospinal fluid (CSF) using VBM5 [6]. After segmentation RAVENS GM/WM/VENT images and registered T_1-weighted images were generated for the baseline ALS and control subject scans using HAMMER [7]. By definition, the voxel intensities of the RAVENS GM/WM/VENT images sum to the patients segmented brain volume prior to registration. To remove patient brain volume as a bias from RAVENS ALS baseline and control images for cross-sectional analysis, the intensities of these images were normalized such that the sum was equal for all of the subjects. For longitudinal analysis, the baseline image for each ALS subject was used as the atlas for generating the RAVENS GM/WM/VENT images. After the RAVENS images were generated, they were registered using the deformation field that was generated during the registration of the baseline images. No normalization was applied to the longitudinal RAVENS images. As a final processing step, all of the images were smoothed with an isotropic 5 mm FWHM Gaussian kernel. The RAVENS images for ALS baseline and control subjects were compared statistically using a paired t-test in SPM5. Areas of significantly decreased volume were identified using an uncorrected p-value of 0.001. For each region of significantly decreased volume, the MARSBAR [8] SPM5 toolbox was used to test for statistical significance longitudinally (see Table 1).

Results:

Significant volume loss was seen in both RAVENS GM and WM images. No significant volume increase was seen in the RAVENS VENT images. Table 1 shows a trend of significant volume loss of WM with respect to disease duration and GM with respect to time of measurement and disease duration. Fig.1 shows the sagittal views of the brain regions listed in Table 1. The average 0.57 per month decrease in ALSFRS-R was significant (p=0.0021).

Discussion:

Localized volume loss was demonstrated using this high resolution VBM technique. The areas of largest volume loss were in the right pre-central gyrus and the right middle temporal gyrus. The left post-central gyrus, right superior parietal lobule, and right middle temporal gyrus were associated with disease duration (*Duration*) and severity (*ALSFRS-R*). White matter losses were also seen as a function of time, which may reflect the different trajectory of neuronal and axonal degeneration. Similar regions were observed in previous cross-sectional and longitudinal studies [1, 9-11].

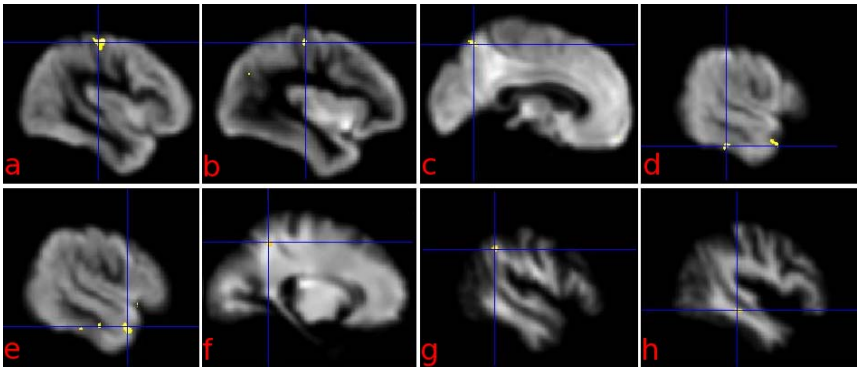

Fig. 1. Sagittal views of brain regions listed in Table 1: a) RPreCG, b) LPostCG, c) RSPL, d) RMTG, e) RMTG, f) LPLWM near left superior parietal lobule, g) LPLWM near left angular gyrus & supramarginal gyrus, and h) RTLWM near middle temporal gyrus. The colored clusters show regions of significant difference for the paired t-test between baseline ALS & normal controls.

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Table 1. p-values and average volume loss for longitudinal ALS RAVENS GM and WM images. *Paired t-test* refers to baseline and 6 month paired t-test, *Time* refers to time since baseline using all time-points correlated with volume, *Duration* refers to disease symptom duration using all time-points correlated with volume, and *ALSFRS-R* is ALS Functional Rating Score-Revised correlated with volume. Average volume loss is shown only for regions that are significant or approach significance (p<0.10).

Tissue	*Brain Region*	*Paired t-test*		*Time*		*Duration*		*ALSFRS-R*	
		p-value	*Volume Loss (mm^3)*	*p-value*	*Volume Loss (mm^3/month)*	*p-value*	*Volume Loss (mm^3/month)*	*p-value*	*Volume Loss (mm^3/score)*
GM (a)	RPreCG	0.410441	-	0.004591	6.2985	0.998379	-	0.793932	-
GM (b)	LPostCG	0.059720	2.6797	0.996625	-	0.054022	0.1550	0.000746	0.4340
GM (c)	RSPL	0.131938	-	0.257703	-	0.001240	0.4895	0.069113	0.4005
GM (d)	RMTG	0.861741	-	0.320083	-	0.032794	0.1580	0.192544	-
GM (e)	RMTG	0.060396	7.1550	0.000545	7.8175	0.235450	-	0.065370	1.1925
WM (f)	LPLWM	0.164747	-	0.035706	2.0915	0.997973	-	0.277481	-
WM (g)	LPLWM	0.048703	2.0915	0.009116	2.1360	0.300570	-	0.059934	0.4005
WM (h)	RTLWM	0.138645	-	0.000013	2.9120	0.758849	-	0.507028	-

RPreCG = right pre-central gyrus, LPostCG = left post-central gyrus, RSPL = right superior parietal lobule, RMTG = right middle temporal gyrus, LPLWM = left parietal lobe WM, RTLWM = right temporal lobe WM