Cross-sectional and Longitudinal Voxel-Based Relaxometry Study in ALS

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Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that destroys both the lower-motor neurons (LMN) and upper-motor neurons (UMN) responsible for voluntary muscle control. Diagnosis of ALS relies on the presence of both UMN and LMN clinical findings [1]. However, autopsy studies demonstrate corticospinal tract (CST) degeneration in more than 50% of ALS subjects who were void of UMN symptoms [2]. As a result, much research has been devoted to ALS UMN biomarker discovery using neuroimaging [3]. Conventional MRI has been studied extensively, but is currently only used to rule out other neurological disorders that mimic ALS symptoms. Less well examined is quantitative T_2 relaxometry, which has the potential to detect small changes in T_2 not seen in standard T_2-weighted images.

The objectives of this study were to identify regions of increased or decreased T_2 in ALS cross-sectionally using whole-brain voxel-based relaxometry (VBR)[4] and determine the relationship of T_2 with time, disease duration from onset of symptoms, and disease severity longitudinally.

Methods

Twelve ALS subjects (8 male and 4 female, average age 52.7 ± 10.6 years, range 37 – 68 years) were recruited at baseline. Seven ALS subjects returned for a follow-up visit approximately 6 months after baseline and 6 subjects at approximately 12 months. For each image date, the ALS Functional Rating Score-Revised (ALSFRS-R) and disease duration from onset of symptoms were recorded. Twelve approximately age and gender matched normal control subjects (6 male and 6 female, average age 53.2 ± 10.9, range 37 – 68 years, P = 0.91) without neurological or neuromuscular diseases were also recruited for the study. All participants were provided written informed consent and approval for human research was obtained from the Institutional Review Board (Penn State College of Medicine IRB Protocol No. 20473).

Images were acquired on a Philips Intera 3.0 Tesla system (Philips Healthcare, Andover, MA, USA) using a body transmit coil and a 6 channel parallel head receive coil. Multi spin-echo images were acquired with 11 echoes, 8 ms starting TE, 8 ms echo spacing, 3000 ms TR, and SENSE factor 2. The in plane matrix size was 256 x 256 and the slice thickness was 4 mm. For image registration purposes, a whole brain T_1-weighted MDEFT image with 3.14 ms TE, 10.55 ms TR, 680 ms TI, SENSE factor 2, 20° flip angle, and 1 mm isotropic spacing was acquired for each subject. T_2-maps were generated using MRIUtil [5], which uses the MR Parameter Map Suite [6]. The non-linear mono-exponential fitting routine based on the Levenberg-Marquardt algorithm [7] was used. Image registration was performed using STAMPS [8]. STAMPS requires a high-resolution T_1-weighted image of each subject to non-linearly register the processed T_2-maps to an atlas. Briefly, the T_1-weighted images were segmented into GM, WM, and cerebrospinal fluid (CSF) using SPM5/VBM5 [9, 10]. After segmentation HAMMER [11] was used to register the segmented images to the HAMMER supplied atlas. As described in [8], the processed T_2-maps are registered to the atlas by first linear registration to the T_1-weighted image using FSL FLIRT and then non-linearly by applying the HAMMER generated deformation field to the linearly registered T_2-maps.

Whole brain voxel-based statistical parametric analysis was performed using SPM5. Prior to analysis all images were smoothed with a 5 mm FWHM Gaussian kernel and an explicit mask was generated as the overlap of each registered image prior to smoothing. For cross-sectional analysis, an ANCOVA model grouped by control and ALS with age as covariate was used for VBR. Significant regions were highlighted by thresholding the statistic maps with a p-value of 0.001 uncorrected and a minimum cluster size of 100 voxels. For longitudinal analysis, two statistical models were examined based on the available longitudinal ALS image data. In both models, the independence option was set to "No", to account for dependency in the repeated measures. First, a paired t-test between baseline and 6 months ALS was performed. The remaining model was a full factorial design grouped by baseline ALS, 6 months ALS, and 12 months ALS with disease duration from onset of symptoms and ALSFRS-R as covariates. Only those subjects that were imaged on all three time points were included in the three groups. Statistically significant brain regions were highlighted by thresholding the statistic maps using a false discovery rate (FDR) of 0.05 and a minimum cluster size of 100 voxels.

Results

Figure 1 shows clusters of significant cross-sectional T_2 differences overlaid on the group averaged smoothed T_2-map. Clusters of significantly increased ALS T_2 when compared with controls were located within the right subcortical medial frontal gyrus (MFG), right superior temporal gyrus, left subcortical superior/medial frontal gyrus, and left MFG. No clusters of significantly decreased T_2 were detected. Of the 2 whole-brain longitudinal models described in the methods section, only disease duration yielded significant clusters. Figure 2 shows clusters of positively correlated disease duration for T_2 overlaid on the average smoothed T_2-map.

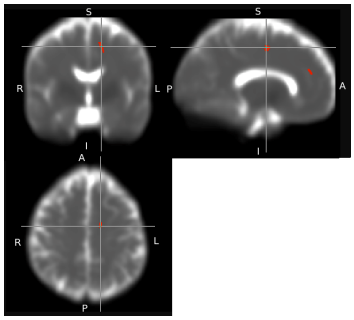

Figure 1. Clusters of significant ALS and control group differences for T_2 relaxometry overlaid on the group averaged smoothed T_2-map image. Clusters shown are within the left subcortical superior/medial frontal gyrus and the left MFG.

Discussion

A previous ALS PET study reported decreased glucose activity in the superior/medial frontal gyrus [12]. In light of this previous finding the increased T_2 in the superior/medial frontal gyrus might be due to cytotoxic edema. Although these regions were not detected on a whole-brain level longitudinally, using the clusters identified cross-sectionally a statistically significant ($P<0.05$) increase in T_2 of approximately 0.15 ms/month was measured for the disease duration model. The increased T_2 observed longitudinally using SPM is most likely due to GM atrophy. Previous longitudinal volume data using the same subjects confirm this conclusion [13]. A larger patient population is needed in order to fully describe the cross-sectional and time-varying characteristics of T_2 in the brain in ALS and can be useful as a tool to monitor the progress and severity of the disease.

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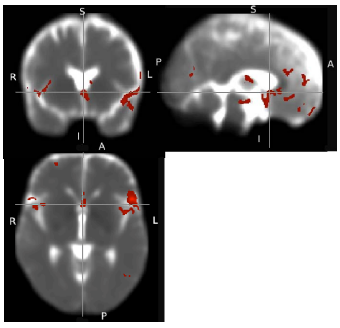

Figure 2. Clusters of significant longitudinal positive correlation of ALS T_2 relaxometry with disease duration from onset of symptoms. The largest clusters occur in the bilateral frontal lobe WM, bilateral inferior frontal gyrus, bilateral cingulate region, and the left superior temporal gyrus.