BRAIN RESEARCH 1348 (2010) 156–164

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Research Report

# Utility of axial and radial diffusivity from diffusion tensor MRI as markers of neurodegeneration in amyotrophic lateral sclerosis

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ARTICLE INFO

*Article history:*
Accepted 24 May 2010
Available online 1 June 2010

*Keywords:*
Amyotrophic Lateral Sclerosis
Magnetic Resonance Imaging
Diffusion Tensor Imaging
Axial diffusivity
Radial diffusivity

ABSTRACT

**Objective:** To investigate changes in the diffusion tensor imaging measures, axial diffusivity and radial diffusivity, in addition to the more commonly used fractional anisotropy and mean diffusivity, in patients with amyotrophic lateral sclerosis (ALS) using the voxel-based statistical analysis tool, tract based spatial statistics. **Methods:** We studied 12 patients with ALS and 19 normal controls using diffusion tensor imaging; tract based spatial statistics was applied to study changes in fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity values in brain white matter tracts. ALS patients were evaluated using clinical examination, administration of the revised ALS functional rating scale and measurement of the forced vital capacity. **Results:** In ALS patients, we found significant increases in axial diffusivity, radial diffusivity, and mean diffusivity and significant decreases in fractional anisotropy. Increases in axial diffusivity and radial diffusivity were more widespread and more prominent in the corticospinal tract than the decreases in fractional anisotropy. The decreases in fractional anisotropy were evident only in the corona radiata and genu of the corpus callosum. **Conclusion:** In ALS, axial diffusivity and radial diffusivity may be useful diffusion tensor imaging-derived indices to consider in addition to fractional anisotropy and mean diffusivity to aid in demonstrating neurodegenerative changes.



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doi:10.1016/j.brainres.2010.05.067

## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by degeneration of both upper and lower motor neurons. Techniques such as electromyography and motor unit number estimation represent useful biomarkers of lower motor neuron dysfunction, but there are currently no biological markers of upper motor neuron dysfunction. Diffusion tensor imaging (Basser et al., 1994) is a non-invasive quantitative magnetic resonance imaging (MRI) method that permits quantification of the directionality of water diffusion, thereby providing information about the micro-structural properties of tissue through which water diffuses. Water diffusion within a highly organized tissue such as white matter is anisotropic as water preferentially diffuses along the axis of white matter tracts.

Axonal degeneration in ALS alters tissue microstructure and hence diffusion of water molecules both perpendicular and parallel to the axonal wall. These changes, which are not evident on conventional MRI, are measurable with diffusion tensor imaging. Sensitivity to microstructure and tissue organization makes diffusion tensor imaging an important tool for studying neurodegenerative disease (Horsfield and Jones, 2002).

With diffusion tensor imaging, one estimates an effective diffusion tensor at each voxel in an image. Several quantities derived from the diffusion tensor include trace, fractional anisotropy, mean diffusivity (Basser and Pierpaoli, 1996), radial diffusivity and axial diffusivity (Basser, 1995). The diffusion tensor is represented by three eigenvectors and corresponding eigenvalues that define an ellipsoid. The trace of the diffusion tensor is the sum of the three eigenvalues while mean diffusivity is the average of the three eigenvalues (mean diffusivity = trace/3) and provides a measure of the degree of restriction to the diffusion of water molecules irrespective of direction (Le Bihan et al., 2001). Conceptually, fractional anisotropy measures the eccentricity, or degree of anisotropy of diffusion (Basser and Pierpaoli, 1996; Basser and Jones, 2002). Fractional anisotropy values range from 0 (isotropic diffusion) to 1 (completely anisotropic diffusion). In anisotropic tissue, such as white matter, the largest eigenvalue represents the diffusivity of water in the direction parallel to the fiber bundles (axial diffusivity). Radial diffusivity, the average of the two smallest eigenvalues, measures water diffusion perpendicular to the axonal wall. Fractional anisotropy and mean diffusivity have been used in the study of a variety of brain white matter pathologies (Mukherjee, 2005; Ge et al., 2005; Kubicki et al., 2005) including primary lateral sclerosis and ALS. There has been little study of the utility of axial diffusivity and radial diffusivity in ALS.

Methods of quantitative diffusion tensor imaging analysis include region-of-interest (ROI) and voxel-based approaches. Tract-based spatial statistics (Smith et al., 2006), the voxel-based approach used in this paper, utilizes extracted and skeletonized white matter tracts in the fractional anisotropy images of all subjects. Tract-based spatial statistics is used in an effort to overcome the problems associated with the use of standard registration algorithms in other voxel-based approaches.

Several investigators have reported reduced fractional anisotropy in the corticospinal tracts of ALS patients although the extent and distribution of these changes have been variable (Ellis et al., 1999; Sach et al., 2004; Graham et al., 2004; Karlsborg et al., 2004; Hong et al., 2004; Cosottini et al., 2005; Smith et al., 2006; Thivard et al., 2007; Wong et al., 2007; Sage et al., 2007; Iwata et al., 2008; Ciccarelli et al., 2009; Sage et al., 2009). Reduced fractional anisotropy along the entire length of the corticospinal tract from the corona radiata through the internal capsule and into the brainstem has been reported using both ROI (Ellis et al., 1999; Cosottini et al., 2005; Iwata et al., 2008) and voxel-based approaches (Sach et al., 2004; Thivard et al., 2007; Sage et al., 2007; Sage et al., 2009). Other reports have described more regionally restricted reductions in fractional anisotropy affecting only the posterior limb of the internal capsule (Graham et al., 2004), the brainstem (Hong et al., 2004; Wong et al., 2007) or a gradient of fractional anisotropy reduction that was most marked in the pons, less prominent in the internal capsule, and normal in the corona radiata (Karlsborg et al., 2004). Inconsistent results were reported in one of the studies that utilized tract-based spatial statistics (Ciccarelli et al., 2009). Furthermore, in a more recent tract-based spatial statistics analysis of subjects included in their first voxel-based study, Sage et al. reported finding reductions in fractional anisotropy in the splenium and body of the corpus callosum in addition to the previously reported reductions in fractional anisotropy in the corticospinal tract (Sage et al., 2009) (Appendix Table 1).

Reported changes in mean diffusivity in ALS patients have been less consistent. Several studies have reported increased mean diffusivity in selected regions of the corticospinal tract of ALS patients—the internal capsule more so than the pons, but not the corona radiata (Karlsborg et al., 2004), and the cerebral peduncles, but not the pons and medulla (Hong et al., 2004). Others found no significant differences in mean diffusivity between patients and controls (Graham et al., 2004; Wong et al., 2007). Cosottini et al. (2005) reported normal axial diffusivity but increased radial diffusivity in ALS patients, indicating normal diffusion along the corticospinal tract but increased diffusion perpendicular to the corticospinal tract. However, Wong et al. (2007) found normal radial diffusivity but increased axial diffusivity only in the corona radiata of ALS patients. Using tract-based spatial statistics, Sage et al. reported finding significant increases in mean diffusivity within the corticospinal tract (Sage et al. 2009) in the same patients they had previously described (Sage et al. 2007) initially not finding those mean diffusivity increases in the corticospinal tract.

In this paper, we report diffusion tensor imaging and tract-based spatial statistics analysis of fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity maps of ALS patients and age-matched controls. We hypothesize that there would be utility in considering axial diffusivity and radial diffusivity in addition to the more commonly considered fractional anisotropy and mean diffusivity to aid in revealing neurodegenerative changes in ALS.

## 2. Results

Of the 12 ALS patients (10 males, 2 females, mean age 56.2 ± 10.5 years), 5 patients were diagnosed with definite ALS according to the El Escorial criteria (Brooks et al., 2000); 2 with probable ALS, 4 with possible ALS, and 1 with familial ALS. Mean revised