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Altered white matter microarchitecture in amyotrophic lateral sclerosis: A voxel-based meta-analysis of diffusion tensor imaging

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ABSTRACT

Background: The results of recent diffusion tensor imaging (DTI) studies on amyotrophic lateral sclerosis (ALS) are inconclusive and controversial. We performed a voxel-based meta-analysis to identify a statistical consensus among published DTI studies of altered white matter (WM) microarchitecture in ALS.

Methods: A systematic search was conducted for relevant studies that used voxel-wise analyses of WM microarchitecture in patients with ALS. Anisotropic effect size-signed differential mapping (AES-SDM) was applied to analyze fractional anisotropy (FA) differences between ALS patients and healthy controls. Meta-regression analysis was used to explore the effects of clinical characteristics on WM integrity in patients with ALS.

Results: A total of 14 studies with 16 datasets that included 396 patients and 360 healthy controls were identified. The pooled meta-analysis revealed that patients with ALS exhibited significant FA reductions in two clusters relative to healthy controls. The largest cluster exhibited a peak coordinate in the left corona radiata, extending to the body and splenium of the corpus callosum, left superior longitudinal fasciculus, posterior limb of the internal capsule, right corona radiata, and bilateral cingulate gyrus. The other cluster exhibited decreased FA in the right corticospinal tract that extended to the right cerebral peduncle. The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) score was positively correlated with the FA reduction in the left corona radiata. Mean age and illness duration were not linearly correlated with the FA reductions.

Conclusions: This study provides a thorough profile of WM microarchitecture alterations in patients with ALS and further evidence that the neuronal degeneration is not limited to the corticospinal tract but also includes extra-motor areas, which supports the view that ALS is a multisystem degenerative disorder that involves the white matter.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative, age-related and predominantly male disease that may result in the progressive loss of bulbar and limb function. **Patients suffer from motor function deteriorated and finally develop fatal respiratory failure (Schmidt et al., 2014).** ALS is a disease with an insidious onset, and there is a long period before typical symptoms begin appearing. The overall lifetime prevalence rate is 1:400, and most patients die within 3–5 years of symptom onset (O et al., 2011). The diagnosis is based on upper and lower motor neuron clinical signs (O et al., 2011). **With the development of imaging technology, magnetic resonance imaging (MRI) is now the leading technique in the search for biomarkers (Turner et al., 2011) and currently assists with the diagnosis of ALS substantially.**

In recent years, psychoradiology (Lui et al., 2016) which studies brain diseases through a variety of non-invasive imaging techniques is emerging. Diffusion tensor imaging (DTI) is a mature and sensitive instrument for detecting WM microarchitecture track alterations. DTI measurements depend on the fractional anisotropy (FA), which is greater in major WM tracks, lower in gray matter, and approaches 0 in cerebrospinal fluid (Smith et al., 2006). A previous study (Thivard

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et al., 2007) demonstrated that FA alterations result from a loss of fiber integrity caused by axonal degeneration as indicated by the lack of volume loss. Diffusion MRI is a promising and non-invasive method to detect the degree of fiber damage in various disease processes that affect WM by measuring FA. There is a large body of evidence highlighting FA changes in ALS that have used voxel-based analyses (VBA) or tract-based spatial statistics (TBSS) methods. However, the results are inconsistent and controversial. According to previous studies, a significant decrease in FA has been observed in patients with ALS in WM regions that include the bilateral corticospinal tract (CST) (Crespi et al., 2014; Kassubek et al., 2014; Senda et al., 2011), corpus callosum (CC) fibers (Agosta et al., 2007; Keil et al., 2012), thalamus (Sach et al., 2004; Thivard et al., 2007), right association fibers (Zhang et al., 2014), right frontal subgyral area and left frontal precentral area (Abe et al., 2004). One study found an FA reduction in the bilateral posterior portion of the corona radiata and the left cerebral peduncle (Zhang et al., 2007). However, another study found FA reductions in the right cerebral peduncle and left posterior limb of the internal capsule (Zhang et al., 2014). An intriguing study (Trojsi et al., 2015) divided ALS patients into 3 stages according to clinical diagnoses and found decreased FA in the body of the CC and the left CST in clinical stage 2A patients, in the left cerebellar hemisphere, brainstem precerebellar nuclei and premotor cortex in clinical stage 2B patients, and in the rostral part of the CSTs, body of the CC, thalamic radiations, bilateral superior and inferior longitudinal and fronto-occipital fasciculi, right uncinate fasciculus and midbrain in clinical stage 3 patients. However, another study found no significant differences in the central part of the CC between patients with ALS and healthy controls (Agosta et al., 2010). Thus, conducting a meta-analysis to identify the most prominent and consistent statistical results from DTI studies of the WM integrity of patients with ALS is necessary.

A previous meta-analysis found FA reductions in the bilateral frontal WM and the posterior limb of the bilateral internal capsule (Li et al., 2012). However, only 8 published DTI studies were included in this meta-analysis, and other confounding factors, such as possible methodological differences between the included studies, were not considered. Additionally, this study did not use meta-regression to investigate the potential moderating effects of clinical characteristics on regional WM abnormalities. Recently, there have been many original studies on this issue. To overcome these limitations and increase our understanding of this neurobiological disorder, we intend to identify and integrate more recent DTI studies for a more comprehensive and rigorous meta-analysis, which will be the most up-to-date meta-analysis available.

Our purposes in conducting this meta-analysis are as follows: first, to quantitatively summarize the 14 most relevant DTI studies (16 datasets met the inclusion criteria) concerning FA abnormalities in patients with ALS using a newly developed meta-analysis technique, anisotropic effect size-signed differential mapping (AES-SDM), which has the potential to quantify the reproducibility of neuroimaging findings and produce insights that are difficult to obtain from individual studies; second, to perform subgroup meta-analyses that include only studies with methodological homogeneity to avoid the potentially confounding effects of different methodologies; third, to use a meta-regression method to assess the potential effects of mean age, age at onset, duration of disease, and ALSFRS-R score on the reported WM abnormalities.

2. Materials and methods

2.1. Literature search strategy

We searched PubMed, EMBASE, Web of Science, Cochrane Library and Science Direct to find relevant literature published articles between January 1994 and November 2016 and “in press” articles. All follow a systematic and extensive retrieval strategy. The search keywords were (“amyotrophic lateral sclerosis” or “ALS”) and (“diffusion tensor” or “DTI” or “diffusion magnetic resonance imaging”). Additionally, the reference lists of both eligible articles and review articles were manually screened to avoid omitting.

2.2. Study selection and data extraction

All studies found in our search were assessed. The studies included in the meta-analysis met all of the following inclusion criteria: (i) original articles published in peer-reviewed English-language journals; (ii) studies comparing the FA values of WM areas between patients with ALS and healthy controls; and (iii) studies that detected FA alterations in whole-brain analyses and reported the results in Talairach or Montreal Neurological Institute coordinates. The corresponding authors of studies that met all of the above inclusion criteria but lacked global brain coordinates were contacted to obtain additional information.

The exclusion criteria for this meta-analysis were as follows: (i) studies that were case reports or reviews; (ii) studies involving familial ALS patients; (iii) studies that lacked an health control group; and (iv) studies using overlapping research samples from different publications (in such cases, the data from the study with the largest sample were included in the meta-analysis). Additionally, our meta-analysis also defers to the guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000).

Two authors extracted from the included studies demographic characteristics (sample size, age, and gender), clinical data (age at onset, illness duration, symptom severity), data processing method, statistical thresholds. **The three-dimensional coordinates in each study were also extracted for the meta-analysis according to the AES-SDM methods (Radua et al., 2014b). Its main feature is the possibility of combining peak coordinates and statistical parameter map, and use of statistical data has been established and the differences between accounting research (Radua et al., 2012b).** The authors did this independently and based on the AES-SDM method (Radua et al., 2014b). Discussions were performed when there are disagreements.

2.3. Voxel-wise meta-analysis

We performed a voxel analysis to identify FA differences between ALS patients and healthy controls, and AES-SDM software was used according to standard procedures. To examine the reproducibility, we performed systematic whole-brain voxel-based jack-knife sensitivity analysis. This method consists of iteratively repeating the pooled meta-analysis while discarding a different data set in each iteration to determine whether a discovery was replicable (Radua et al., 2014a). We also performed several subgroup meta-analyses to analyze methodological differences between these studies. This analysis included only the studies with methodological homogeneity, which was repeated for those studies that used VBA or TBSS approaches, for those that used statistical parametric mapping (SPM) and the functional MRI of the brain (FMRIB) software library (FSL) or tensor imaging and fiber tracking (TIFT) software, and for those with corrected or uncorrected thresholds.

All analytical processes above were based on the AES-SDM tutorial (http://sdmproject.com/software/Tutorial.pdf) and previous literature (Radua et al., 2014a). The parameters of AES-SDM were as follows: anisotropy = 1.0; isotropic full-width at half-maximum (FWHM) = 20 mm; peak height threshold = 1; voxel $p = 0.005$; and cluster extent = 10 voxels with 10 repetitions of standard randomization tests. Furthermore, to convert the AES-SDM results into imaging, we used MRIcron software (http://www.cabiatl.com/mricro/mricron/), and the results were overlaid on a high-resolution brain image template created by the International Consortium for Brain Mapping. The WM bands were plotted with DTI query software (http://graphics.stanford.edu/projects/dti/) by displaying the brain regions with significant FA differences and by means of a map of the human WM