Journal of Neuroscience Methods 224 (2014) 79–87

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Tractography in amyotrophic lateral sclerosis using a novel probabilistic tool: A study with tract-based reconstruction compared to voxel-based approach

Alessia Sarica[c,1], Antonio Cerasa[a,b,*,1], Roberta Vasta[a], Paolo Perrotta[a], Paola Valentino[b], Graziella Mangone[a], Pietro H. Guzzi[c], Federico Rocca[a], Matteo Nonnis[a], Mario Cannataro[c], Aldo Quattrone[a,b]

[a] IBFM, National Research Council, Germaneto, Catanzaro, Italy
[b] Institute of Neurology, University "Magna Graecia", Germaneto, Catanzaro, Italy
[c] Department of Medical and Surgical Sciences, Magna Graecia University of Catanzaro, Italy

HIGHLIGHTS

- TRACULA is a sensitive tool for detecting white matter changes in ALS.
- TRACULA reveals white matter abnormalities in the corticospinal and cingulum tracts.
- TRACULA has the potential to be translated in clinical practice.

ARTICLE INFO

Article history:
Received 11 July 2013
Received in revised form
19 November 2013
Accepted 30 December 2013

Keywords:
TRACULA
DTI
Tractography
Amyotrophic lateral sclerosis
Corticospinal tract

ABSTRACT

Background: Diffusion tensor imaging (DTI) is one of the most sensitive MRI tools for detecting subtle cerebral white matter abnormalities in amyotrophic lateral sclerosis (ALS). Nowadays a plethora of DTI tools have been proposed, but very few methods have been translated into clinical practice.
New method: The aim of this study is to validate the objective measurement of fiber tracts as provided by a new unbiased and automated tractography reconstruction tool named as TRActs Constrained by UnderLying Anatomy (TRACULA). The reliability of this tract-based approach was evaluated on a dataset of 14 patients with definite ALS compared with 14 age/sex-matched healthy controls. To further corroborate these measurements, we used a well-known voxelwise approach, called tract-based spatial statistics (TBSS), on the same dataset.
Results: TRACULA showed specific significant alterations of several DTI parameters in the corticospinal tract of the ALS group with respect to controls.
Comparison with existing method: The same finding was detected using the well-known TBSS analysis. Similarly, both methods depicted also additional microstructural changes in the cingulum.
Conclusions: DTI tractography metrics provided by TRACULA perfectly agree with those previously reported in several post-mortem and DTI studies, thus demonstrating the accuracy of this method in characterizing the microstructural changes occurring in ALS. With further validation (i.e. considering the heterogeneity of other clinical phenotypes), this method has the potential to become useful for clinical practice providing objective measurements that might aid radiologists in the interpretation of MR images and improve diagnostic accuracy of ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive atrophy and weakness of the limbs and of the bulbar and respiratory muscles caused by the impairment of both the upper motor neuron (UMN) and the lower motor neuron (LMN) (Rowland, 1998). Nowadays, the diagnosis

Abbreviations: ALS, amyotrophic lateral sclerosis; DTI, STAI, diffusion tensor imaging; TRACULA, TRActs Constrained by UnderLying Anatomy; TBSS, tract-based spatial statistics; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity; FA, fractional anisotropy.

* Corresponding author at: Neuroimaging Unit, National Research Council (CNR), Viale Europa, 88100 Germaneto (CZ), Italy. Tel.: +39 0961 3695904; fax: +39 0961 3695919.
E-mail address: a.cerasa@unicz.it (A. Cerasa).
[1] These authors equally contributed to this work.

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http://dx.doi.org/10.1016/j.jneumeth.2013.12.014

of ALS is predominately based only on clinical features (i.e., electromyography) and through the exclusion of other diseases with similar symptoms. At the same time, the role of conventional magnetic resonance imaging (MRI) is limited. In fact, MRI is currently used only to exclude other pathologies rather than confirming the diagnosis. For this reason, there is a great interest in defining new *in vivo* objective biomarkers that might significantly impact clinical management and practice; for instance, clinical evaluation alone is insufficient in distinguishing among certain ALS-related syndromes.

Diffusion tensor MR imaging (DTI) is one of the most sensitive and promising MRI-based diagnostic tools for detecting microstructural cerebral white matter changes in ALS. DTI is a non-invasive magnetic resonance method based on the diffusion characteristics of water, which recognises where the motion of water molecules is less random and restricted by biological barriers (such as axonal membrane or axonal microtubule). This non-random type of water movement is referred to as “anisotropic diffusion” (Pierpaoli and Basser, 1996; Chenevert et al., 1990), and water tends to diffuse along a preferential axis that coincides with the orientation of ordered structures, such as axonal tracts. The information contained in the DTI is usually contracted into two types of parameters: diffusion anisotropy, which represents the amount of directionality; and orientation of the axis along which water molecules move preferentially (Wakana et al., 2003). This can be described mathematically by a tensor, which is characterized by its three eigenvectors ($\lambda 1$, $\lambda 2$, $\lambda 3$) and the corresponding eigenvalues. The eigenvector associated with the largest eigenvalue indicates the predominant orientation of fibers in the given voxel. These neuroimaging measures provided fundamental information about white matter integrity that is generally obscure in radiological investigations.

The vast majority of DTI studies in ALS patients have been performed using either a region-of-interest (ROI) or a voxelwise approach. In conventional MRI, neuroradiologists manually draw an ROI to extract quantitative metrics from DTI maps. A major limitation of this approach is the ability to accurately determine the actual boundaries of the fiber tracts to avoid partial volume contamination from other fibers. This may lead to site selection bias, resulting in additional interobserver variability in the measurements. A better method to overcome these limits is to employ advanced DTI-based tractography to map the fiber orientation and use this as an unbiased guide for ROI placement (defined as “seed-based” approach). Several sophisticated neuroimaging methods have been proposed in recent years to reconstruct white matter architecture of the human brain (Wakana et al., 2003; Mori and Zhang, 2006; Ciccarelli et al., 2008; Catani et al., 2012). In the diffusion tractography approach the reconstruction of fibers starts from a seed point and proceeds following different techniques. The so-called deterministic method infers the pathway voxel by voxel, reconstructing one fiber at a time. Otherwise, the probabilistic approach returns multiple trajectories evaluating the estimate of probability distribution. This later method aims to overcome the limitations of deterministic tractography, such as the variability in geometry and topology, as a function of the chosen starting point. Overall, tractography methods may also be categorized considering the existence of an end point to construct the streamline. If no specific target regions have been fixed, tractography is defined as local, while if the streamline is constrained from a starting and ending point, tractography is defined as global. The first works using probabilistic tractography algorithms were mainly interested in extracting sensible fiber tracts specifically involved in the pathophysiological mechanisms of ALS. In particular, Ciccarelli et al. (2006) demonstrated that patients with a rapid disease progression rate had significantly lower connectivity measurements than controls in the corticospinal tract. Very recently, the deterministic approach was applied to an ALS population by using q-ball tract-based spatial statistical analysis with deterministic tractography of genu, body, and splenium of corpus callosum and corticospinal tracts (Caiazzo et al., 2013). These authors highlighted the role played by the callosal integrity (characterized by significant reduction in both fiber density and volume and increase in tract length) as a consistent feature of most ALS variants, significantly related to both pyramidal dysfunction and disease disability.

Another widely employed DTI approach for investigating the neuroanatomical correlates of ALS is the voxelwise analysis (Agosta et al., 2007; Thivard et al., 2007; Metwalli et al., 2010). However, many of these publications contain inconsistent and controversial results because of small and heterogeneous samples of participants, as well as substantial methodological differences between studies (for a review, see Li et al., 2013). Indeed, one major limitation of this kind of approach is that optimal analysis is compromised by the use of standard registration algorithms. In fact, there has not been a satisfactory solution to the question of how to align FA (or MD, RD) images from multiple subjects in a way that allows for valid conclusions to be drawn from the subsequent voxelwise analysis. To solve part of these issues, recently Smith et al. (2006) proposed a new tool, called tract-based spatial statistics (TBSS). TBSS is one of the most frequently cited group analysis streams in neuroimaging community available as part of the FSL software suite from the FMRIB group at Oxford (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). TBSS aims to improve the sensitivity, objectivity, and interpretability of voxelwise analysis via (a) carefully tuned nonlinear registration, followed by (b) projection onto an alignment-invariant tract representation (the “mean DTI metric skeleton”). Overall, although TBSS has been extensively employed to define the presence of white matter abnormalities in ALS patients (Ciccarelli et al., 2009; Filippini et al., 2010; Menke et al., 2012; Prudlo et al., 2012; Prokscha et al., 2013), the findings provided by all voxelwise approaches speak about the pathophysiological mechanisms underlying ALS.

With this in mind, it is important to highlight that despite the large amount of evidence demonstrated by all these research studies, among all these proposed advanced neuroimaging approaches (ROI-based, seed-based, voxelwise) very few methods have currently been translated into clinical practice.

Recently, a new method providing an unbiased and automated reconstruction of the major white matter pathways has been developed by the Martinos center for Biomedical Imaging of Boston (Yendiki et al., 2011) named as TRACULA (TRActs constrained by underlying anatomy). TRACULA uses global probabilistic tractography (Jbabdi et al., 2007) based on the knowledge of prior distributions of the neighboring structures of each pathway, derived from a set of training subjects. At this moment, a preliminary validation of this tool has been performed on a schizophrenic population revealing high reliability and accuracy in the measurement of the principal white matter fiber tracts (Yendiki et al., 2011), but a validation in a neurological realm has not yet performed.

For this reason, the aim of this study is to validate this new DTI-based tool, which may have the potential to be applied in the clinical practice of ALS. The fact that TRACULA provides *per se* a completely automated and unbiased reconstruction of the main human fiber tracts speaks about the potential application of this method in neurological/radiological practice, as an alternative to time-consuming, operator-dependent ROI-based and voxelwise approaches. To corroborate our analysis, we compare the performance of TRACULA to that derived from TBSS. Our primary goal is to demonstrate the accuracy of TRACULA to detected white matter abnormalities in the fiber tracts specifically affected in ALS patients (such as the corticospinal tract and the cingulum, for a review see Li et al., 2012) and to speculate on the possible application of this method in clinical practice.