Clinicial Investigative Study

Comparison of Diffusion Tensor-Based Tractography and Quantified Brain Atrophy for Analyzing Demyelination and Axonal Loss in MS

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ABSTRACT

We combined diffusion tensor imaging (DTI) measures of the corpus callosum (CC) and the superior longitudinal fascicle (SLF) with calculation of brain atrophy in 53 patients with relapsing—remitting multiple sclerosis (MS) and 15 healthy controls, to analyze their interrelation and their correlation with disease duration and clinical impairment. The lateral ventricle volume in MS patients was increased; the fractional anisotropy in the CC was decreased as was the fiber volume. Perpendicular (in the literature also referred to as radial) diffusivity (ped), which reflects the diffusion perpendicular to the long axis of the axons within the fiber bundle, was increased in the SLF and the posterior CC, but contrary to our predictions, parallel (also called axial) diffusivity (pad) that refers to the amount of diffusion in the direction of the axon was increased, too. Brain atrophy and DTI-derived parameters were highly intercorrelated and both correlated with disease duration. Discriminant analysis showed that DTI-derived atrophy measures are superior to brain atrophy measures in classifying patients and controls. In light of our results, animal studies focusing on demyelination and axonal loss are reinterpreted.

Keywords: Multiple sclerosis, diffusion tensor imaging, tractography, brain atrophy, parallel and perpendicular diffusivity.

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Introduction

In the western hemisphere multiple sclerosis (MS) is the most common central nervous system disease in young adults leading to disability. The pathophysiological interpretation of MS has changed from demyelination of the white matter into a demyelinating and degenerative disease process of white and gray matter and many studies in recent years focused on this interplay. Inflammation, demyelination, gliosis, and axonal degeneration are pathological hallmarks of MS. Conventional clinical magnetic resonance imaging (MRI) scanning gives only a crude measure of axonal damage (via visual inspection of brain atrophy), but axonal damage is presumably the main cause for functional impairment and low quality of life. Therefore, more sensitive and specific methods are needed to identify axonal damage to monitor disease progression and to determine efficacy of putative neuroprotective agents.

Quantifying brain atrophy is a well-established method for measuring neurodegeneration and the accompanying functional impairments in MS.[1,2] Brain atrophy starts early in the disease process, and can be detected already in the patients with isolated clinical symptoms. Brain atrophy increases in patients with a verified diagnosis of MS[3] and correlates not only with physical impairments,[4] but also with cognitive deficits[5] and fatigue.[6] Although there are several methods to estimate the extent of brain atrophy,[7] it has been demonstrated that they are reliable and lead to comparable results. Because estimation of brain atrophy is based on MRI sequences (T1 and/or fluid-attenuated inversion recovery) used in clinical routine, it has become a widespread method and has been accepted as a surrogate marker in drug approval studies.[8]

More recently, diffusion tensor imaging (DTI) has also been used to examine normal appearing white matter (for reviews, see[9-14]), and quite a number of studies found significant differences in brain areas with normal-appearing white matter, showing that this method might be sensitive to neuropathological alterations, not detectable with conventional MRI. One interesting possibility of DTI is to track fiber bundles in the brain by clustering voxels according to the value of their major or dominant diffusion tensor. This allows to focus the neuroradiological analysis on different intracortical connections, which are known to be involved often in MS pathology, as, for example, the corpus callosum (CC) or the superior longitudinal fascicle (SLF), which is located adjacent to the lateral ventricle (ie, "periventricularly").[15] Such a focusing might help to overcome indirect measures of axonal degeneration as global and central brain atrophy. It has been argued that the calculation of the

