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Increased cortical curvature reflects white matter atrophy in individual patients with early multiple sclerosis

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ABSTRACT

Objective: White matter atrophy occurs independently of lesions in multiple sclerosis. In contrast to lesion detection, the quantitative assessment of white matter atrophy in individual patients has been regarded as a major challenge. We therefore tested the hypothesis that white matter atrophy (WMA) is present at the very beginning of multiple sclerosis (MS) and in virtually each individual patient. To find a new sensitive and robust marker for WMA we investigated the relationship between cortical surface area, white matter volume (WMV), and whole-brain-surface-averaged rectified cortical extrinsic curvature. Based on geometrical considerations we hypothesized that cortical curvature increases if WMV decreases and the cortical surface area remains constant.

Methods: In total, 95 participants were enrolled: 30 patients with early and advanced relapsing–remitting MS; 30 age-matched control subjects; 30 patients with Alzheimer's disease (AD) and 5 patients with clinically isolated syndrome (CIS).

Results: 29/30 MS and 5/5 CIS patients showed lower WMV than expected from their intracranial volume (average reduction 13.0%, $P < 10^{-10}$), while the cortical surface area showed no significant differences compared with controls. The estimated WMV reductions were correlated with an increase in cortical curvature ($R = 0.62$, $P = 0.000001$). Discriminant analysis revealed that the curvature increase was highly specific for the MS and CIS groups (96.7% correct assignments between MS and control groups) and was significantly correlated with reduction of white matter fractional anisotropy, as determined by diffusion tensor imaging and the Expanded Disability Status Scale. As expected by the predominant gray *and* WM degeneration in AD, no systematic curvature increase was observed in AD.

Conclusion: Whole-brain-averaged cortical extrinsic curvature appears to be a specific and quantitative marker for a *WMV–cortex disproportionality* and allows us to assess "pure" WMA without being confounded by intracranial volume. WMA seems to be a characteristic symptom in *early* MS and can already occur in patients with CIS and should thus be considered in future MS research and clinical studies.

1. Introduction

1.1. Clinical background

Multiple sclerosis is a chronic, multifocal, demyelinating disorder of the CNS with progressive neurodegeneration caused by autoimmune-inflammatory components. MRI characteristics of the disease include multifocal white matter (WM) and gray matter (GM) lesions, brain atrophy, pseudoatrophy, and occult changes in normal-appearing WM and GM (Pirko et al., 2007; Zivadinov, 2007; Zivadinov et al., 2008), highlighting the pathological significance of measures beyond lesion number and volume (Miller et al., 2002). Visualizing and measuring tissue loss in the CNS of patients with multiple sclerosis presents challenges, as it is inevitably easier to capture an image of conspicuous matter, such as in tumor identification, than it is to capture the absence

Abbreviations: 3D, three-dimensional; CI, confidence interval; CIS, clinically isolated syndrome; DTI, diffusion tensor imaging; EDSS, Expanded Disability Status Scale; EVAL, Münster Neuroimaging Evaluation System; eWMV, estimated white matter volume; FA, fractional anisotropy; FOV, field of view; GM, gray matter; GMV, gray matter volume; GRAPPA, generalized autocalibrating partially parallel acquisition; ICV, intracranial volume; ROI, region of interest; SD, standard deviation; TE, echo time; TR, repetition time; TSE, turbo spin-echo; WM, white matter; WMV, white matter volume; ΔWMV, WMV − eWMV.

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of matter due to the disappearance of myelin sheaths, axonal loss, or cell death.

Reduction in brain volume can occur by distinct mechanisms, including inflammatory processes, such as brain oedema, and neurodegenerative events, such as the loss of myelin or axons. There is a vast amount of evidence supporting the hypothesis that pathological changes in WM volume (WMV) may occur by mechanisms that are at least partly independent of overt lesion genesis in early multiple sclerosis (Chard et al., 2002; Filippi et al., 2012). The loss of WM, specifically, is considered to be of high pathophysiological relevance and not an epiphenomenon. Brain atrophy, which can be detected very early in the disease course of multiple sclerosis, is strongly related to disability, but is not well reflected by lesion load when examined in larger cohorts (Calabrese et al., 2007; De et al., 2010; Popescu et al., 2013; Turner et al., 2003).

1.2. Overall hypothesis

With the evolution of more sophisticated imaging techniques, the opportunity exists to identify new, increasingly sensitive measures of tissue loss. Such a novel tissue loss-sensitive biomarker would need to avoid any confounding effects of intracranial volume (ICV), absolute brain size, or absolute CSF volume, and would have to reflect actual microstructural changes of the WM as well as functional deficits of the patients. One concept for such a "new" marker was inspired by an everyday life observation (Fig. 1): that an object with signs of minimal volumetric "atrophy" would have an increased extrinsic (mean) surface curvature if the surface area remains largely constant while the volume is reduced. Thus, it was hypothesized that measuring the extrinsic curvature of the cortex may provide a reliable measure of underlying WM atrophy.

1.3. Why measuring curvature to assess a volume?

The idea here was not to assess any absolute or relative volume. The idea was to assess a potential volumetric *change* of the WM with a single time point MRI. An *initial* (single time point) WMV estimation can principally not be used to ensure (slight) atrophy. By definition, *atrophy* is an *acquired* volume loss, but an initially estimated WMV is not related to any earlier volume. Thus we questioned if we could find a measure that must have changed from a normal value to an obviously (quantitatively) altered value if the WM selectively has shrunk in the past? As a potential candidate, we identified the cortical curvature. However, if the analogy to the apple of Fig. 1 should hold, a number of *prerequisites* must be fulfilled. We have to show that: (i) the WM volume is lower in patients with MS, (ii) the cortical surface *area* is not proportionally altered relative to healthy controls, (iii) the cortical curvature of healthy subjects has less variation than the WMV, and (iv) a volume lower than expected from normal controls is correlated with a higher curvature.

Fig. 1. Representative object (apple) with signs of minimal volumetric "atrophy". The wrinkled skin has an increased *extrinsic* curvature.

1.4. Objective and clinical hypotheses

The objective of the present study was to investigate whether the cortical extrinsic curvature could represent a new, robust, and sensitive biomarker to assess loss of WM brain parenchyma in an early stage of multiple sclerosis.

In this context, we tested the following clinical hypotheses:

- The WM is more affected than suggested by inspecting MRI slices visually, even in patients with clinically isolated syndrome (CIS) or early relapsing–remitting multiple sclerosis.
- Curvature as an atrophy marker is correlated to microstructural alterations of the WM.
- The cortical extrinsic curvature (a geometric measure) is possibly a more sensitive structural marker for selective WM atrophy than WMV itself.

2. Materials and methods

2.1. Structure and concept of the study

To test the prerequisites to establish increased cortical curvature as marker for a volumetric *change* (Section 1.3, i–iv) and to test our clinical hypotheses, we performed a study that was structured into the following analyses.

In *Analysis I*, we estimated WMV and GM volume (GMV) in a cohort of patients with early and advanced relapsing–remitting multiple sclerosis (the multiple sclerosis group), age-matched control subjects (the control group) and patients with expected high atrophy of the WM and GM due to their age and a neurodegenerative condition (the Alzheimer's disease group). We were interested in how the expected WM atrophy of the relatively young patients with multiple sclerosis was quantitatively related to the atrophy observed in the Alzheimer's disease group. We further questioned how the absolute WMVs were related to (and thus confounded by) the individual ICVs. To test the hypothesis that effects seen in the multiple sclerosis group could principally also occur in individuals who are potentially in a "pre-state" of multiple sclerosis, we also included five patients with CIS (*Part I-a*). In *Part I-b* of the study, we examined individual cortical GM measures, i.e. the cortical GMV, cortical thickness, and cortical surface area of all participants.

Analysis II aimed to answer the question whether a potential WM–GM disproportion would correlate with an increased cortical extrinsic curvature as demonstrated by the apple in Fig. 1 (*Part II-a*), and, if so, if this increase would be specific to the patients in the multiple sclerosis group (*Part II-b*), and how age, disease duration, and lesion load would be related to any potential curvature alteration (*Part II-c*). *Analysis III* should reveal if any potential geometric properties of the cortex are associated with intrinsic microstructural alterations of the WM as they can be determined by diffusion tensor imaging (DTI).

Analysis IV should clarify if an increase in the cortical extrinsic curvature has any functional correlate, i.e. is related to the disease progression as expressed by the Expanded Disability Status Scale (EDSS) (*Part IV-a*), and, if so, whether this measure would better correlate with the EDSS than the estimated individual volumetric loss of WM brain