NeuroImage: Clinical 4 (2014) 10–17

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Jacobian integration method increases the statistical power to measure gray matter atrophy in multiple sclerosis☆

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ARTICLE INFO

Article history:
Received 30 July 2013
Received in revised form 2 October 2013
Accepted 23 October 2013
Available online 29 October 2013

Keywords:
Multiple sclerosis
Magnetic resonance imaging
Gray matter
Atrophy
Sample size
Jacobian integration

ABSTRACT

Gray matter atrophy provides important insights into neurodegeneration in multiple sclerosis (MS) and can be used as a marker of neuroprotection in clinical trials. Jacobian integration is a method for measuring volume change that uses integration of the local Jacobian determinants of the nonlinear deformation field registering two images, and is a promising tool for measuring gray matter atrophy. Our main objective was to compare the statistical power of the Jacobian integration method to commonly used methods in terms of the sample size required to detect a treatment effect on gray matter atrophy. We used multi-center longitudinal data from relapsing–remitting MS patients and evaluated combinations of cross-sectional and longitudinal pre-processing with SIENAX/FSL, SPM, and FreeSurfer, as well as the Jacobian integration method. The Jacobian integration method outperformed these other commonly used methods, reducing the required sample size by a factor of 4–5. The results demonstrate the advantage of using the Jacobian integration method to assess neuroprotection in MS clinical trials.

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system. Although multiple focal lesions in white matter are the pathologic and imaging hallmarks of MS, gray matter is also involved. Gray matter pathology, which has been known from early post-mortem studies (Dawson, 1916) but overlooked for many decades, has recently become a new focus of MS research (Kutzelnigg et al., 2005; Lucchinetti et al., 2011). Several postmortem (Bo et al., 2007; Kutzelnigg et al., 2005), in vivo magnetic resonance imaging (MRI) (Mainero et al., 2009), and MR spectroscopy studies (Caramanos et al., 2009) have shown that gray matter pathology appears to be independent of white matter pathology, suggesting distinct mechanisms of tissue destruction. Pathological studies have shown that there is significant gray matter demyelination in MS, the extent of which can exceed that of white matter (Geurts et al., 2012; Kutzelnigg et al., 2005). However, cortical lesions are rarely visible on conventional MRI (Geurts et al., 2005a, 2008). Advanced MRI techniques such as double inversion recovery and phase-sensitive inversion recovery can improve sensitivity to leukocortical and intracortical lesions (Geurts et al., 2005b; Nelson et al., 2007) but fail to capture the large bands of subpial demyelination seen on histopathology (Seewann et al., 2012). Tissue loss in gray matter (gray matter atrophy), which apparently results from lesional as well as non-lesional pathology (Wegner et al., 2006) and represents overall destructive pathology including neurodegeneration, can be measured by conventional MRI.

Measures of cortical gray matter tissue loss or atrophy are clinically relevant, as they correlate with cognitive impairment (Amato et al., 2007), are more closely associated with physical disability than whole brain atrophy (Fisher et al., 2008), and appear to be less influenced by so-called "pseudoatrophy" than whole brain or white matter atrophy (Nakamura et al., 2010; Tiberio et al., 2005). Indeed, these properties make cortical gray matter atrophy attractive as an outcome measure in clinical trials, particularly as therapeutic targets shift from suppression of inflammation to neuroprotection and remyelination.

The longitudinal measurement of cortical volume change on MRI is not an easy task because the cortex is thin and convoluted, and the relaxation behavior of both cortex and white matter can change with pathology. To be useful as an outcome measure in MS, it is critical to determine an optimal strategy to quantify gray matter atrophy with high statistical power. The objectives of this study were: (1) to assess the reproducibility of various analysis pipelines to measure cortical or gray matter volume, (2) to quantify cortical or gray matter atrophy over

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http://dx.doi.org/10.1016/j.nicl.2013.10.015

time in an MS population, (3) to compare these pipelines in terms of required sample size, and (4) to assess factors in study design (image resolution and study duration) that influence the statistical power to detect a clinical effect on the rate of cortical atrophy over time.

2. Material and methods

We used a scan–rescan dataset to calculate reproducibility and a longitudinal clinical study of MS patients to measure the required sample sizes to detect gray matter atrophy.

2.1. Subjects

Subjects for the scan–rescan dataset were 20 healthy normal controls (age = 30 ± 4 years, 10 females) (Aubert-Broche et al., 2006). Subjects for the longitudinal dataset came from a multi-center clinical study (Assessment Study of Steroid Effect in Relapsing Multiple Sclerosis Subjects Treated with Glatiramer Acetate, ASSERT, NCT00203047) involving 414 relapsing–remitting MS (RRMS) patients. A cohort of 287 patients (mean baseline age = 39.9 ± 9.0, proportion of female = 73.2%) who completed at least two MRI sessions was studied here. All patients were randomized to either with glatiramer acetate alone or with glatiramer acetate plus 1250 mg of prednisone given orally for 5 days every 4 months.

2.2. Imaging

The scan–rescan MRIs were previously obtained T1-weighted 3D spoiled gradient-recalled echo images [echo time (TE) = 9.2 ms, repetition time (TR) = 22 ms, flip angle (FA) = 30°, resolution = $1.0 \times 1.0 \times 1.0$ mm^3]. The images were acquired twice on the same day from 1.5 Tesla Siemens Sonata Vision scanner.

The longitudinal data were acquired at 63 different clinical sites using 1.0 T (n = 2), 1.5 T (n = 57), or 3.0 T (n = 4) scanners. The manufacturers included Philips (n = 15), Siemens (n = 18), General Electric (n = 25), and Marconi (n = 5). Relevant MRI sequences included: (a) axial proton density (PD)-weighted spin echo [TE = 10–17 ms, TR = 2000–3800 ms, in-plane resolution = 0.977×0.977 mm^2, slice thickness = 3 mm], (b) axial T2-weighted spin echo images [TE = 77–96 ms, TR = 3267–7767 ms, in-plane resolution = 0.977×0.977 mm^2, slice thickness = 3 mm], (c) sagittal high-resolution 3D T1-weighted gradient echo image [TE = 4–10 ms, TR = 15–24 ms, FA = 30°, resolution = $1.5 \times 1.0 \times 1.0$ mm^3], and (d) axial standard-resolution 3D T1-weighted gradient echo image [TE = 5–11 ms, TR = 28–34 ms, FA = 30°, resolution = $1.0 \times 1.0 \times 3.0$ mm^3]. Subjects were scanned annually for up to 3 years.

2.3. Segmentation of MS lesions

T2-lesions in white matter were automatically segmented using a multispectral Bayesian classifier (Francis, 2004) with PD-weighted, T2-weighted, and T1-weighted images, and then reviewed by experts and manually corrected as necessary. No cortical gray matter lesions were identified, as the scanning sequence was not designed to be sensitive to gray matter lesions.

2.4. Image analysis

The T1-weighted images for each subject were analyzed by combinations of cross-sectional and longitudinal pre-processing with cross-sectional segmentation-based and longitudinal registration-based algorithms. The following section describes the details of the pre-processing and atrophy measurement methods. All methods were fully-automated except for the MS-lesion segmentation described above.

Conventional cross-sectional pre-processing (XPP): As shown in Fig. 1, XPP consisted of (XPP-1) N3 intensity-non-uniformity correction (Sled et al., 1998); (XPP-2) MS-lesion filling (Battaglini et al., 2012) (to reduce bias in gray matter volumes due to the impact of variable white matter MS lesion loads on image intensity distributions) (Nakamura and Fisher, 2009); and (XPP-3) standard ICBM-space registration (using the ICBM 2009c Nonlinear Symmetric Template) (Fonov et al., 2009), using a hierarchical registration technique (Nakamura, 2011). Briefly, the hierarchical registration procedure involved estimating the affine transformation parameters in multiple steps: (1) two rotations (y- and z-rotations) by maximizing the left and right inter-hemispheric symmetry, (2) x-rotation and z-translation by normalized mutual information (NMI) registration to align anterior–posterior on the y-axis, (3) multi-seed optimization for a global scaling factor using NMI, and (4)

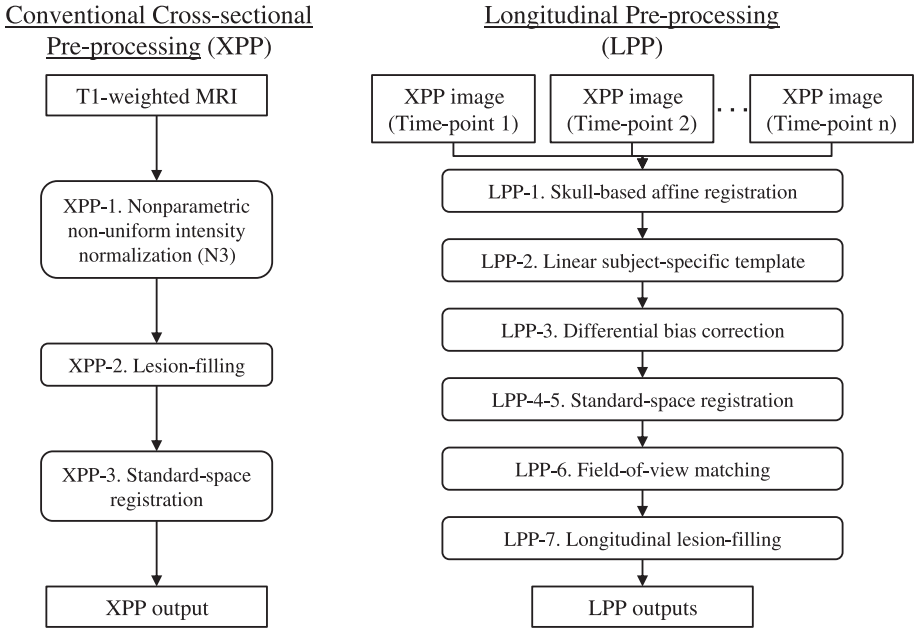

Fig. 1. Flowchart describing the cross-sectional (XPP) and longitudinal (LPP) pre-processing pipelines.