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Regional brain atrophy development is related to specific aspects of clinical dysfunction in multiple sclerosis

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Brain atrophy in multiple sclerosis (MS) is thought to reflect irreversible tissue damage leading to persistent clinical deficit. Little is known about the rate of atrophy in specific brain regions in relation to specific clinical deficits.

We determined the displacement of the brain surface between two T1-weighted MRI images obtained at baseline and after a median follow-up time of 2.2 years for 79 recently diagnosed, mildly disabled MS patients. Voxel- and cluster-wise permutation-based statistics were used to identify brain regions in which atrophy development was significantly related to Expanded Disability Status Scale (EDSS), Timed Walk Test (TWT), Paced Auditory Serial Addition Test (PASAT) and 9-Hole Peg Test (HPT). Clusters were considered significant at a corrected cluster-wise *p*-value of 0.05.

Worse EDSS change-score and worse follow-up EDSS were related to atrophy development of periventricular and brainstem regions and right-sided parietal, occipital and temporal regions. Worse PASAT at follow-up was significantly related to atrophy of the ventricles. A worse TWT change-score and worse follow-up TWT were exclusively related to atrophy around the ventricles and of the brainstem. Worse HPT change-score and worse follow-up HPT of either arm were significantly related to the atrophy of widely distributed peripheral regions, as well as atrophy of periventricular and brainstem regions.

Our findings suggest that decline in ambulatory function is related to atrophy of central brain regions exclusively, whereas decline in neurologically more complex tasks for coordinated hand function is related to atrophy of both central and peripheral brain regions.

Introduction

Progressive brain atrophy is a well-known feature of multiple sclerosis (MS) and in vivo quantification of brain atrophy using MRI is increasingly used to study the disease evolution of MS (Miller et al., 2002). Previous studies have found that brain atrophy in MS occurs early in the disease course (Brex et al., 2000) is related to MR measures reflecting axonal degeneration (De Stefano et al., 2002) and is predictive of clinical functioning at long-term follow-up (Fisher et al., 2002).

An association between global measures of disability and overall brain atrophy has been established (Kalkers et al., 2001), probably reflecting clinically important neurodegenerative changes. Beyond this overall association, atrophy of specific regions of the brain is likely to be related to specific clinical functional deficits. Few previous studies have investigated atrophy of selected brain structures in MS in relation to clinical deficit. For instance, more clinical disability and higher lesion load have been related to ventricular enlargement in early relapsing remitting MS (Brex et al., 2000; Dalton et al., 2002). Furthermore, poorer performance on neuropsychological tests has been related to atrophy of the corpus callosum (Pelletier et al., 2001) and frontal lobes (Locatelli et al., 2004). Regarding cortical gray matter, several recent studies have shown that cortical thickness decreases over time and is related to progressing clinical disability (Charil et al., 2007; Chen et al., 2004; Sailer et al., 2003).

Recent technical advances have provided a number of automated analysis techniques for longitudinal brain volume change. SIENA is an automated registration-based analysis technique that calculates the percentage brain volume change between two scans based on local brain edge displacement, integrated over the whole brain (Smith et al., 2002). Using voxel-wise statistical analysis, the local brain edge displacement calculated by SIENA can be used to study regional aspects of brain atrophy development over time in relation to clinical characteristics. Using this approach, one study found that

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regional brain atrophy rate is different between MS phenotypes and is related to more overall clinical disability as measured by the EDSS (Pagani et al., 2005).

In this study we aimed to investigate, in a relatively large group of recently diagnosed MS patients, the relationship between regional atrophy development and specific aspects of clinical dysfunction, reducing differences in brain geometry and using non-parametric voxel-wise statistics.

Materials and methods

Patients

From a cohort of 133 recently diagnosed (Poser et al., 1983) MS patients enrolled in an ongoing natural history study, patients with a relapse onset type of disease and complete MRI were selected. Written informed consent was obtained from all participating patients and our local ethics review board approved the study. From the original cohort, 37 patients were excluded because a suitable MRI scan was not available both at baseline and at follow-up, 16 patients were excluded because they had a progressive onset type of disease and for one patient clinical examination could not be performed at one time point. Hence, a total of 79 patients were included in this study.

Clinical and MRI examinations were performed at the time of diagnosis, referred to as the baseline examination, and after a median time of 2.2 years (Inter Quartile Range [IQR]: 2.0–2.4 years), referred to as the follow-up examination. When patients had a relapse, clinical and MRI evaluations were delayed for a minimum of 6 weeks. Decisions to start disease-modifying therapy (DMT) were made by the treating neurologist according to guidelines for standard clinical practice.

Well-trained raters assessed patient disability at both visits using Kurtzke's Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) and the MS Functional Composite (MSFC) scale, consisting of the Timed Walk Test (10-m version) (TWT), 9-Hole Peg Test (HPT) and the Paced Auditory Serial Addition Test (3-s version) (PASAT) (Cutter et al., 1999). The overall MSFC score was calculated using a previously published reference population of MS patients (Kalkers et al., 2000). "Annualised" changes in the clinical measures were calculated by dividing the difference between baseline and follow-up scores by the time between measurements. A negative value indicates worsening for the EDSS, TWT, HPT and MSFC, and improvement for the PASAT. We will use the term "worsening on" with respect to any of the clinical scales to indicate a clinically less favourable change on that scale. The MRI analyses in which relations with individual MSFC components were investigated (described below) were restricted to patients with complete MSFC examinations at both time points ($n=74$).

MR acquisition and pre-processing

Baseline and follow-up MRI examinations were performed on a 1.0-T MRI scanner (Magnetom Impact, Siemens AG, Erlangen, Germany) and included axial 2D spin echo T1-weighted imaging without administration of contrast agent (repetition time [TR]: 700 ms, echo time [TE]: 15 ms, number of slices: 25, slice thickness: 5 mm, interslice gap: 0.5 mm, in-plane resolution: 1.0 by 1.0 mm). T2 lesion load (T2LL) was quantified using home-developed semi-automated seed growing software based on a local thresholding technique after lesion identification by an expert reader.

For each patient, the Percentage Brain volume Change (PBVC) for the entire brain between baseline and follow-up was determined using SIENA software (Smith et al., 2002) with the T1-weighted images as input. A negative PBVC indicates 'atrophy' of the brain, whereas a positive PBVC indicates 'growth' of the brain. SIENA estimates the PBVC by registering the baseline and follow-up MR image and subsequently determining the displacement of the brain edge between these two scans. Since not all scans included the full brain due to differences in head size, the SIENA analysis was restricted to a pre-specified interval along the *Z*-axis, ranging from −52 mm to +60 mm in standard MNI152 space.

Besides the PBVC, SIENA generates a 3D image that represents local brain edge displacement for each voxel of the brain surface between the baseline and follow-up scan, from now on referred to as the "brain edge displacement map". For the voxel values of the brain edge displacement map, negative values indicate motion toward the brain parenchyma (i.e., 'atrophy'), whilst positive values indicate motion away from the brain parenchyma (i.e., 'growth'). The magnitude of the values indicates the distance by which the brain edge has moved in millimetres.

For voxel-wise statistical analysis we roughly followed the scheme proposed by Bartsch et al. (2007), also described on the FSL website (http://www.fmrib.ox.ac.uk/fsl/). In brief, to allow voxel-wise statistics, the following pre-processing steps were performed on the brain edge displacement maps of each subject: (1) all voxel values within the brain edge displacement map were divided by the time between scans in years (annualised). (2) The brain edge displacement map was dilated, reducing differences in brain surface geometry. (3) The original full view MR images used to determine the edge displacement map were affinely registered to the MNI152 standard image. The spatial transformation obtained was then used to register the dilated displacement map to MNI152 standard space. Visual inspection of all registrations confirmed that they were acceptable. (4) The image was limited to a pre-specified interval along the *Z*-axis, ranging from −52 mm to +60 mm in standard MNI152 space (i.e., as used in the original SIENA analysis). (5) The image was masked by the pre-defined brain edge mask supplied in FSL 3.2 (Smith et al., 2004). (6) The image was smoothed with a 10-mm FWHM Gaussian filter and re-masked with the same pre-defined brain edge mask.

Statistical analysis

Whole-brain atrophy and descriptive variables

PBVC values were divided by the time between scans to obtain the annualised PBVC (PBVC/y). Comparisons of variables between patient groups (defined by DMT status or sex) were performed using the Mann–Whitney *U*-test. Differences in clinical measures between baseline and follow-up over the entire group were tested using the Wilcoxon signed-rank test. Spearman rank correlation was used to test the relationship of annualised PBVC with clinical disability measures, baseline age in years and baseline disease duration in years, as well as the cross correlations between clinical scales. A *p*-value of 0.05 was considered statistically significant and none of the conventional statistical analysis methods were corrected for multiple comparisons. All analyses were performed using SPSS 12.0.1.

Voxel- and cluster-wise cross-subject statistical analyses

All voxel- and cluster-wise analyses were performed by means of cross-subject permutation-based non-parametric voxel-wise statistics (Nichols and Holmes, 2002), implemented using Randomise