T2-maps of normal appearing brain tissue show clusters of voxels correlating with neuropsychological test results in MS

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Introduction

Although we know the neuropsychological impairments seen in multiple sclerosis (MS)[1] to be caused by pathological changes in the central nervous system, there is an only moderate correlation between neuropsychological test results and conventional magnetic resonance imaging[2]. However, such studies often use measures of T2 lesion load, thus ignoring possible T2 changes in the *normal appearing brain tissue* (NABT). In the present study, we address whether T2-changes in NABT can explain part of the neuropsychological impairment seen in MS. We approach this question by applying a large battery of neuropsychological measures and by using the working hypotheses (i) that the degree of pathology is on a continuous scale rather than in discrete steps, (ii) that some anatomical areas might be more prone to cause neuropsychological impairment and (iii) that pathology is not confined to focal lesions. For comparison, we report results from a more conventional approach investigating correlations between total lesion volume and neuropsychological measures.

Patients and Methods

We retrospectively studied 50 newly diagnosed patients (38 female, 12 male) with clinically definite MS. Their mean (SD) age was 35.9 (9.4) years, *expanded disability status scale* (EDSS) 2.6 (1.3) and *multiple sclerosis impairment scale* (MSIS) 13.2 (12.5).

We used a battery of 32 neuropsychological tests grouped in eight cognitive domains (mental processing speed, verbal fluency, visuospatial memory, complex motor speed, visual problem solving, working memory, verbal intelligence and simple motor speed). In addition to these eight domains we included a *cognitive dysfunction factor* (CDF) based on neuropsychological tests best distinguishing impaired patients from healthy controls.

Due to the retrospective nature of the study, the used MR-protocols vary. Scans were obtained at a field strength of 1.0 (11 subjects) or 1.5 (39 subjects) tesla. Whole-brain double (turbo) spin echo sequences were obtained for each patient. Sequence parameters were: TE1: 15 - 45 ms, TE2: 80 - 98 ms and TR: 2.0 - 3.7 s.

Lesion maps were constructed semi-automatically based on tissue-classification by visual inspection of proton density (PD) and T2-weighted images, and total lesion load was tested for correlation with the score in each of the eight domains, the CDF as well as the clinical measures EDSS and MSIS.

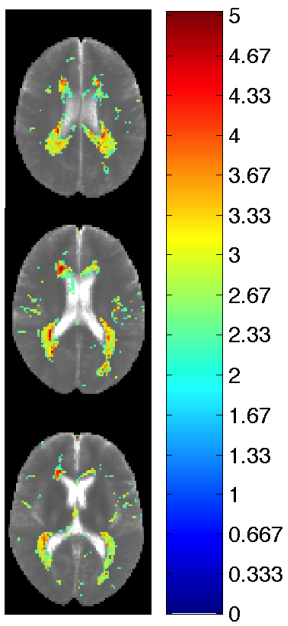
T2 values were calculated as T2 = (TE1 - TE2)/ log(Sig2 / Sig1), where Sig1 and Sig2 are the signal values at echo times TE1 and TE2, respectively.

The second echoes were used for spatial normalization to a standard T2 template. Using SPM2 (www.fil.ion.ucl.ac.uk/spm/software/spm2/) we applied an affine transformation with 12 parameters. T2 and lesion maps were subsequently resliced to 96 slices with an in-plane resolution of 2 mm x 2 mm. Voxel-based analyses were used to test for correlations between T2 value and the score in each of the eight domains as well as CDF. We used a general linear model with the following covariates: a) patient age, b) scanner/sequence combination and c) the investigated neuropsychological measure. Voxels classified as lesion were excluded from the analysis on a subject basis.

Results

We found a significant, positive correlation between total lesion volume for each patient and CDF ($r = 0.34$, $p = 0.02$), mental processing speed ($r = 0.34$, $p = 0.03$), complex motor speed ($r = 0.39$, $p = 0.01$), visual problem solving ($r = 0.40$, $p = 0.01$) and verbal intelligence ($r = 0.40$, $p = 0.005$). No significant correlations with EDSS or MSIS were found.

We found distinct clusters of voxels whose T2-values correlate with mental processing speed (see figure), CDF (maps not shown) as well as complex motor speed (maps not shown). Correlations found on the map of simple motor speed were negligible (maps not shown). For the other cognitive domains only minor clusters of correlation, primarily bilaterally and posterior to the ventricles were found (maps not shown).



The color layers illustrating the p-value are thresholded at p = 0.01 and clusters shown have a minimum size of 10 voxels. Values shown next to the color bars are the negative logarithm of the p-values. Clusters of correlation are layered on top of the T2 template used for registering. For clarity only three slices are shown.

Discussion and Conclusion

In the present study T2 in NABT showed areas of significant correlation with neuropsychological scores. This suggests that T2-changes in NABT caused by an underlying pathology can explain part of the neuropsychological impairment seen in MS. Furthermore, T2 lesion load showed correlation to the same neuropsychological scores, but not to the EDSS or MSIS. This may be illustrating the inadequacy of the clinical scores to capture the actual impairment of the patient.

It is intriguing that the correlations we find in this voxel-based analysis are to measures evaluating speed of performance. Indeed, it has lately been acknowledged that speed more than number of correct answers is a key aspect of the neuropsychological impairment[3]. To the best of our knowledge, this study is the first voxel-based investigation of correlations between T2 values of NABT and neuropsychological measures of impairment in MS. The practical relevance for large-scale studies was demonstrated, as results were obtained using conventional sequences from various sites and vendors.

References

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