qMT imaging to assess brain tissue modifications in patients with Miotonic Dystrophy type-1.

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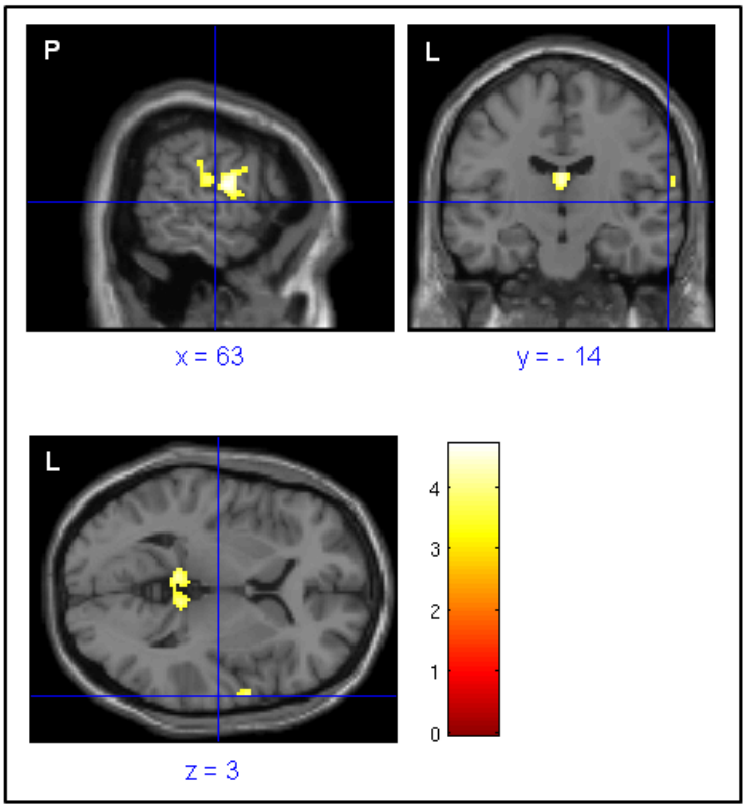
INTRODUCTION

Myotonic dystrophy type 1 (MD1), the most common form of adult muscular distrophy, is an autosomal dominant progressive multisystem disorder characterized by muscular atrophy, myotonia, frontal baldness, cataract, gonadal atrophy, cardiac disorders, and endocrine abnormalities [1]. A number of neuroimaging studies have evaluate the relevance of brain involvement in MD1. In particular, MRI studies have demonstrated that focal white matter (WM) lesions can be found frequently in the brains of MD1 patients. There is not, however, full agreement on the significance and extent of these WM lesions and while some studies found a relationship between the extent of WM lesions and patients' clinical status, most studies did not find this correlation. Moreover, a significant number of MD1 patients seem to show no abnormalities on conventional MRI despite their clinical signs of CNS involvement. A number of in vivo and ex vivo studies have stressed the importance of WM pathology in MD1 and this has been interpreted as due to increases of interfascicular space, cellular infiltrates and breakdown of myelin sheaths. However, several studies also have shown that abnormalities can extend well beyond the focal areas of hyperintensity detected on conventional MRI and that diffuse brain atrophy can occur in patients with MD1, with similar involvement of WM and GM. In agreement with this, the importance in MD1 of a diffuse pathology that significantly involves the GM has been stressed by several neuropathological studies showing specific signs of neuronal damage such as neurofibrillar tangles and hyperphosphorylated tau proteins in the cerebral cortex [2]. More recently, Giorgio et al. [2] using magnetization transfer (MT) imaging showed, with respect to normal controls, lower cortical-MT ratio and higher cortical atrophy in MD1 patients with no or minimal WM abnormalities on conventional MRI, supporting the hypothesis of the presence of neocortical pathology in MD1. They also showed absence of significant differences between MD1 patients and normal controls in both WM-MT ratio and normal-appearing white values (NWMV) further supporting this hypothesis and suggesting that cortical abnormalities may occur with a mechanism that is not related to that of focal WM lesion formation. MT generates contrast dependent upon the exchange of magnetization between semi-solid macromolecular hydrogen nuclei, such as protein structures and cell membranes, and free water protons, allowing these macromolecules (whose relaxation times are too short to be imaged directly) to be indirectly probed. The MT effect is usually quantified by generating MT ratio images, which provide voxel by voxel maps of the percent decrease in signal caused by the MT saturation pulse. However, MTR changes can also be affected by non-specific changes in water content or physical state, such as may be associated with inflammation [3,4]. In order to overcome some of the limitations of the MTR measure, a more complete characterization of the MT phenomenon has been developed. Using this new technique, it is now possible to produce parametric images of all the observable properties of the binary spin bath model for MT: the relative size of the macromolecular pool, or F; the forward magnetization exchange rate, or RM_0^B; the transverse relaxation time of the macromolecular pool, T_2^B. This methodology has been termed ''quantitative magnetization transfer imaging'' or qMTI [5]. Aim of this study was to o evaluate the sensitivity of qMT imaging to the subtle brain tissue changes in subjects with MD1, by using a voxel-wise approach.

METHODS

We recruited 21 MD1 patients [F/M=10/11; mean (SD) age=40.0 (9.2) years] with no or minimal abnormalities visible on conventional MRI, and 21 sex- and age-matched healthy controls [HS, F/M=10/11; mean (SD) age=37.4 (9.8) years]. All subjects underwent a neuropsychological examination and an MRI acquisition at 3.0T. The MRI session included for every subject: (1) a Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR= 1338 ms, TE= 2.4 ms, Matrix= 256 x 224, n. slices= 176, thick. 1 mm); (2) a series of 12 MT-weighted 3D FLASH sequences (TR= 35 ms, TE= 7.4, flip angle= 7°) with various combinations of amplitude and offset frequency of the MT pulse, optimised according to [6]; (3) three 3D FLASH sequences with variable flip angle for T1 mapping [7]; (4) three 3D FLASH sequences with near-180° flip angles for B_1 mapping [8]. Images from sequences (2)-(4) were used to compute the qMT parameters on a voxel-by-voxel basis [8]: T_1 and B_1 maps were obtained as described in [7] and [8], respectively; then, we fitted Ramani's model [10] of MT to the data of sequence (2) to compute maps of R_A, F, T_2^B, and RM_0^B (where R_A is the longitudinal relaxation rate of the liquid pool, F= M_{0B}/M_{0A}, is the relative size of the macromolecular pool, T_2^B is the transverse relaxation time of the macromolecular pool and RM_0^B is the forward exchange rate). The largest flip angle scan from sequence (3) was used to compute the transformation from native to MNI space, which was then applied to all qMT parametric maps. qMT maps were smoothed with a 6 mm Gaussian kernel. To assess between groups differences in the normalized and smoothed RM_0^B, F and T_2^B maps, we performed two different ANCOVA analysis for each qMT map, one confined in GM and the other in WM, using SPM8 (www.fil.ion.ucl.ac.uk/spm).

Figure 1



RESULTS

The only qMT parameter which showed significant ($p<0.05$, FWE cluster level corrected) between-group differences was RM_0^B in GM. These differences were located bilaterally in the cingulum, in right and in the left thalamus, in the right postcentral cortex and in the right temporo-parietal cortex (Fig1). No other significant results were obtained.

DISCUSSION

Our results show that among qMT parameters, RM_0^B is the most sensitive to MD1 pathology. Data reported in the present study support the hypothesis that cortical damage can be significant in MD1 patients even when they have no or minimal abnormalities visible on conventional MRI. In contrast, signs of subtle and/or diffuse WM abnormalities are not found in these patients [2]. In conclusion these results support the notion that significant neocortical damage can be evident even in the absence of WM lesions and can proceed in parallel with disease duration suggests that a neocortical pathology, unrelated to WM lesion formation, occurs and is clinically relevant in the brains of patients with MD1.

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