The brain in myotonic dystrophy 1 and 2: evidence for a predominant white matter disease

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Myotonic dystrophy types 1 and 2 are progressive multisystemic disorders with potential brain involvement. We compared 22 myotonic dystrophy type 1 and 22 myotonic dystrophy type 2 clinically and neuropsychologically well-characterized patients and a corresponding healthy control group using structural brain magnetic resonance imaging at 3 T (T1/T2/diffusion-weighted). Voxel-based morphometry and diffusion tensor imaging with tract-based spatial statistics were applied for voxel-wise analysis of cerebral grey and white matter affection ($P_{\text{corrected}} < 0.05$). We further examined the association of structural brain changes with clinical and neuropsychological data. White matter lesions rated visually were more prevalent and severe in myotonic dystrophy type 1 compared with controls, with frontal white matter most prominently affected in both disorders, and temporal lesions restricted to myotonic dystrophy type 1. Voxel-based morphometry analyses demonstrated extensive white matter involvement in all cerebral lobes, brainstem and corpus callosum in myotonic dystrophy types 1 and 2, while grey matter decrease (cortical areas, thalamus, putamen) was restricted to myotonic dystrophy type 1. Accordingly, we found more prominent white matter affection in myotonic dystrophy type 1 than myotonic dystrophy type 2 by diffusion tensor imaging. Association fibres throughout the whole brain, limbic system fibre tracts, the callosal body and projection fibres (e.g. internal/external capsules) were affected in myotonic dystrophy types 1 and 2. Central motor pathways were exclusively impaired in myotonic dystrophy type 1. We found mild executive and attentional deficits in our patients when neuropsychological tests were corrected for manual motor dysfunctioning. Regression analyses revealed associations of white matter affection with several clinical parameters in both disease entities, but not with neuropsychological performance. We showed that depressed mood and fatigue were more prominent in patients with myotonic dystrophy type 1 with less white matter affection (early disease stages), contrary to patients with myotonic dystrophy type 2. Thus, depression in myotonic dystrophies might be a reactive adjustment disorder rather than a direct consequence of structural brain damage. Associations of white matter affection with age/disease duration as well as patterns of cerebral water diffusion parameters pointed towards an ongoing process of myelin destruction.
and/or axonal loss in our cross-sectional study design. Our data suggest that both myotonic dystrophy types 1 and 2 are serious white matter diseases with prominent callosal body and limbic system affection. White matter changes dominated the extent of grey matter changes, which might argue against Wallerian degeneration as the major cause of white matter affection in myotonic dystrophies.

Keywords: myotonic dystrophy; neuropsychology; MRI; DTI; VBM
Abbreviations: BDI = Beck Depression Inventory; DTI = diffusion tensor imaging; KFSS = Krupp’s fatigue severity scale; PSQI = Pittsburgh sleep quality index; VBM = voxel-based morphometry

Introduction

Myotonic dystrophy types 1 and 2 are autosomal dominantly inherited, progressive multisystemic disorders. Myotonic dystrophy type 1 is the most common form of muscular dystrophy in adults. Both types are caused by untranslated nucleotide repeat expansions in two distinct genes leading to RNA pathology and aberrant alternative splicing of several genes (Day and Ranum, 2005). While myotonic dystrophy type 1 results from a CTG repeat expansion in the dystrophia myotonica-protein kinase gene (DMPK), a CCTG repeat expansion in the zinc finger protein 9 gene (ZNF9) has been identified in myotonic dystrophy type 2 (Brook et al., 1992; Liquori et al., 2001). In myotonic dystrophy type 1, the classic disease range of CTG repeat numbers is 50–4000, in which repeat sizes of 50–80 may be associated with mild clinical phenotypes, and large repeat expansions up to 4000 are often found in severe, mostly congenital forms of the disorder.

There is ample evidence of cerebral involvement in myotonic dystrophy type 1 and 2, albeit less severe in type 2 (Machuca-Tzili et al., 2005; Meola and Sansone, 2007). Mental impairment, executive dysfunctioning and avoidant personality traits—eventually deteriorating with age—have been described in myotonic dystrophy types 1 and 2 (Meola et al., 2003; Gaul et al., 2006; Modoni et al., 2008; Weber et al., 2010). Sleepiness and fatigue constitute major complaints in myotonic dystrophy type 1 and type 2 (Giubilei et al., 1999; Laberge et al., 2009a, b; Tieleman et al., 2010). The pathogenesis of CNS symptoms is not entirely clear. Neurofibrillary degeneration with intraneuronal accumulation of abnormally modified microtubuli-associated tau protein has been demonstrated in the brains of patients with myotonic dystrophy type 1 and 2 (Sergeant et al., 2001; Maurage et al., 2005; Itoh et al., 2010). Aberrant tau expression by dysregulated alternative splicing has been proven in myotonic dystrophies allocating these disorders to a subset of neurodegenerative diseases termed tauopathies (Jiang et al., 2004; Day and Ranum, 2005; Maurage et al., 2005; Leroy et al., 2006; Dhaenens et al., 2008; Ghinem et al., 2009). Brain involvement in myotonic dystrophy types 1 and 2 has been demonstrated in vivo using different neuroimaging techniques. MRI studies revealed white matter lesions and diffuse brain atrophy in myotonic dystrophy types 1 and 2. White matter lesions located within anterior temporal lobes represent a characteristic feature in myotonic dystrophy type 1 (Hund et al., 1997; Kassubek et al., 2003; Kornblum et al., 2004; Romeo et al., 2010). Cellular markers in magnetic resonance spectroscopy were reduced in occipital and temporoparietal cortical regions as well as frontal white matter of patients with myotonic dystrophy types 1 and 2 (Vielhaber et al., 2006). Single photon emission CT and PET studies demonstrated hypoperfusion and glucose hypometabolism of frontal and temporal lobes in myotonic dystrophy type 1, more so than in type 2 (Meola et al., 1999; Weber et al., 2010).

In myotonic dystrophy type 1, grey matter reductions have been described in various cortical regions and recently also in hippocampi and thalami using voxel-based morphometry (VBM) (Antonini et al., 2004; Weber et al., 2010). T2 relaxometry, diffusion MRI studies applying diffusion tensor imaging (DTI), and magnetization transfer imaging showed white matter changes in myotonic dystrophy type 1 using region of interest-based approaches (Di Costanzo et al., 2001; Naka et al., 2002; Fukuda et al., 2005). Atrophy or hypoplasia of the corpus callosum had been described mainly in the congenital disease form of myotonic dystrophy type 1, but a recent diffusion MRI study applying DTI showed widespread white matter abnormalities in congenital, as well as patients with juvenile-onset myotonic dystrophy type 1 (Hashimoto et al., 1995; Wozniak et al., 2011). Giubilei et al. (1999) reported corpus callosum atrophy in a small group of adult patients with myotonic dystrophy type 1. Analysing the regional structural changes of the corpus callosum by the diffusion tensor in DTI, a previous diffusion MRI study found associations with volume loss in corresponding cortical regions. Thus, Wallerian degeneration was postulated as a major cause of white matter affection in myotonic dystrophy type 1 (Ota et al., 2006).

In patients with myotonic dystrophy type 2, we recently demonstrated callosal body affection applying VBM, while grey matter reduction was present in hypothalamic, thalamic and brainstem regions (Minnerop et al., 2008). Weber et al. (2010) found reduced grey matter volumes in their myotonic dystrophy type 2 sample in several cortical regions, including hippocampi and thalami.

While some studies showed correlations of brain morphological changes with neuropsychological and clinical parameters including CTG repeat sizes in myotonic dystrophy type 1 (Ota et al., 2006; Kuo et al., 2008; Romeo et al., 2010; Weber et al., 2010; Wozniak et al., 2011), others failed to do so (Kassubek et al., 2003; Antonini et al., 2004; Fukuda et al., 2005; Di Costanzo et al., 2008).
Disconnection of cortical regions by changes of the interconnecting white matter is a potential mechanism for cognitive dysfunction in various neurological disorders (Dineen et al., 2009), and may also be responsible for CNS symptoms in myotonic dystrophies. Imaging techniques differ regarding their ability to investigate white matter alterations. VBM allows a voxel-wise analysis independent of predefined regions of interests, but it is based on signal differences of grey and white matter in T1-weighted MRIs with a methodological-based focus for grey matter. Contrary, DTI is a qualitative technique that measures tissue properties, i.e. diffusivity and the directional dependence of microscopic diffusion of water molecules in the brain especially in white matter (Catani, 2006). In white matter, diffusion is usually hindered by the high degree of structural organization, resulting in anisotropic movement of water molecules predominantly parallel to the orientation of fibre tracts. A lower fractional anisotropy signifies less anisotropic diffusion and thus lower microstructural integrity (Basser and Jones, 2002). While previous diffusion MRI studies allowed only a region of interest-based analysis of fractional anisotropy values, the new technique ‘tract-based spatial statistics’ enables a voxel-wise analysis of the microstructural integrity of white matter across subjects (Smith et al., 2006).

For a comprehensive analysis of brain structure alterations in myotonic dystrophies, we examined the brains of 22 myotonic dystrophy type 1 and 22 myotonic dystrophy type 2 clinically and neuropsychologically well-characterized patients and a corresponding healthy control group with structural MRI. White matter lesions were rated visually on T2-weighted images, and voxel-based analyses of T1-weighted and diffusion-weighted images (VBM and DTI/tract-based spatial statistics) were applied.

We hypothesized that white matter abnormalities and callosal body affection are present in adult patients with both myotonic dystrophy types 1 and 2 and are more frequent and pronounced as previously suggested. We further aimed to analyse if abnormal white matter integrity was associated with distinct clinical parameters and neuropsychological performance; and whether brain morphological changes play a direct causative role in the development of mood disturbances and increased daytime sleepiness or fatigue. Finally, we intended to evaluate the influence of age and disease duration on brain structural damage to further examine the hypothesis of premature ageing in myotonic dystrophies.

### Materials and methods

#### Subjects

All analyses were performed in 22 patients with myotonic dystrophy type 1 (male/female: 9/13, age 43.1 ± 12.6 years, disease duration 13.2 ± 7.0 years) and 22 patients with myotonic dystrophy type 2 (male/female: 12/10, age 52.5 ± 10.1 years, disease duration 11.9 ± 9.9 years) as well as age- and sex-matched healthy controls (male/female: 11/11, age 50.0 ± 10.2 years). Congenital or infantile-onset forms of myotonic dystrophy type 1 were excluded from this study. Diagnoses were confirmed by genetic testing in all cases. CTG repeat expansion sizes were determined in all patients with myotonic dystrophy type 1 (mean ± SD 614 ± 306, range 80–1100 repeats). None of the patients and control subjects had a past medical history of other neuromuscular or CNS disorders. All subjects underwent clinical–neurological examinations and neuropsychological testing. Education was assessed as a combination score of graduation and professional qualification (sum score), in which score points were given for each school year (up to 13 in Germany), and 3–5 points for the professional qualification (professional education and/or study). In myotonic dystrophy type 1, the Muscular Impairment Rating Scale was used to assess disease severity (Mathieu et al., 2001). Evaluated scales for the assessment of disease severity or muscular symptoms are not yet available in myotonic dystrophy type 2. Characteristics of patients and controls are given in Table 1.

The local ethics committee approved the study protocol. Informed written consent was obtained from all participants.

#### Neuropsychological testing

Cognitive functioning was assessed in patients and controls using a comprehensive neuropsychological test battery. We applied several questionnaires to assess increased daytime sleepiness and fatigue as well as depression. Since motor function affected the majority of neuropsychological test performances, we included the bimanual task of the ‘Pegboard Puzzle’ (Tiffin, 1987; lower values corresponding to a worse test result) as covariate to correct for motor impairment in test performance. MRI correlation analyses were restricted to those clinical and neuropsychological parameters with a significant difference compared with controls.

A detailed description of the test battery together with extensive information on statistical analyses of clinical and neuropsychological data is provided in the Supplementary material.

#### Table 1 Clinical characteristics of patients with myotonic dystrophy type 1 and myotonic dystrophy type 2 and healthy controls (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Myotonic dystrophy type 1 patient group</th>
<th>Myotonic dystrophy type 2 patient group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Age</td>
<td>43.1 ± 12.6*</td>
<td>52.5 ± 10.1</td>
<td>50.1 ± 9.0</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/13</td>
<td>12/10</td>
<td>11/11</td>
</tr>
<tr>
<td>CTG repeat length (range)</td>
<td>614 ± 306 (80–1100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Educational level</td>
<td>10.3 ± 2.6*</td>
<td>11.6 ± 2.1</td>
<td>11.7 ± 1.8</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>13.2 ± 7.0</td>
<td>11.9 ± 9.9</td>
<td>–</td>
</tr>
<tr>
<td>Severity of disease (Muscular Impairment Rating Scale)</td>
<td>3.6 ± 0.9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Motor performance (Purdue Pegboard bimanual, cut-off &lt;11 pairs in 30s)</td>
<td>9.5 ± 2.5*</td>
<td>10.3 ± 1.9*</td>
<td>11.6 ± 1.3</td>
</tr>
<tr>
<td>Depressed mood (BDI score, cut off &gt;10)</td>
<td>9.3 ± 7.8*</td>
<td>8.7 ± 7.2*</td>
<td>2.1 ± 3.5</td>
</tr>
</tbody>
</table>

Educational levels were assessed as a combination score of graduation and professional qualification (sum score).

*P < 0.05, i.e. significant difference compared with control group.
Magnetic resonance imaging
We acquired all MRI data at the Life & Brain Centre Bonn, Germany, using a 3 T scanner (Magnetom Trio, Siemens). An eight-channel head coil was used for signal reception. All subjects underwent the same imaging protocol consisting of whole brain T1-weighted, T2-weighted and diffusion-weighted imaging using an in-house DTI sequence. The total study time was ~40 min per subject, and all images were obtained in one session. Further details of MRI data acquisition are given in the Supplementary material. Image quality was controlled by visual inspection, and images with artefacts were excluded from further data analysis.

Grading of white matter hyperintensities
White matter lesions (≥5 mm) were quantified on T2-images according to the age-related white matter change score (ARWMC; Wahlund et al., 2001), which was used in myotonic dystrophy types 1 and 2 recently (Romeo et al., 2010). The grading within five regions, separately for each hemisphere, ranged from 0 (no lesions) to 3 (diffuse involvement of the entire region).

Voxel-based morphometry
Image processing and statistical analyses were carried out according to the optimized VBM protocol (Ashburner and Friston, 2000; Good et al., 2001) using MATLAB 7.4.0 and statistical parametric mapping (SPM 5; http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Further details of VBM analysis are described in the Supplementary material. Using the smoothed tissue segments, we performed two-sample t-tests comparing each patient group with controls, separately for grey and white matter. The results were explored at a false discovery rate-corrected threshold of P < 0.05 at voxel-level with an extended cluster threshold of 10 voxels.

Diffusion tensor imaging
Preprocessing and analysis of diffusion data were done with an in-house protocol using FMRIB software library (FSL) 4.1.3 tools (available at www.fmrib.ox.ac.uk/fsl). A diffusion tensor was reconstructed, and the following indices were generated using DTfit (Smith et al., 2004): fractional anisotropy, mean diffusivity, eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) of the diffusion tensor with axial diffusivity ($\lambda_3$) presumed to be the diffusivity parallel/along the axon, and radial diffusivity ($[\lambda_2 + \lambda_3]/2$) presumed to be the diffusivity perpendicular to the axon. For voxelwise analysis of the resulting maps, we used the tract-based spatial statistics (version 1.1) tool also included in FSL (Smith et al., 2006). Statistical analysis included (i) group comparisons using two-sample t-tests between myotonic dystrophy type 1/myotonic dystrophy type 2 groups and healthy controls with respect to fractional anisotropy, mean diffusivity, axial and radial diffusivity (P(threshold < 0.05) and (ii) correlation analyses (only for fractional anisotropy maps) in both patient groups, using simple regression models with clinical parameters as determining regressors (P(threshold-free cluster enhancement < 0.05). Further details of DTI data analysis are given in the Supplementary material.

Results

Clinical characteristics of myotonic dystrophy types 1 and 2
Patients with myotonic dystrophy type 1 were younger than controls (P = 0.04), had poorer motor performance (lower values indicating worse performance in the bimanual pegboard task, P = 0.001), fewer years of education (P = 0.049) and higher Beck Depression Inventory (BDI) scores (Hautzinger et al., 1995) indicating more depressive symptoms (P = 0.001), although the group mean score value was still below the clinical cut-off (BDI score 9.3 ± 7.8). BDI scores above the clinical cut-off were found in 7/22 patients with myotonic dystrophy type 1 (32%).

Patients with myotonic dystrophy type 2 did not differ from controls with respect to age and education, but showed poorer motor performance (P = 0.011) and higher BDI scores (P = 0.001). Although the group mean score value was still below the clinical cut-off (BDI score 8.7 ± 7.2), clinically relevantly elevated BDI scores were found in 8/22 patients with myotonic dystrophy type 2 (38%).

Patients with myotonic dystrophy types 1 and 2 did not differ from controls regarding sex distribution. Further, in both patient groups age did not correlate with disease duration, and BDI scores were not associated with age, disease duration or motor performance. In patients with myotonic dystrophy type 1, CTG repeat lengths did not correlate with age, disease duration, muscular impairment rating scale, motor performance or BDI scores.

Comparing patient groups, patients with myotonic dystrophy type 1 were younger than patients with myotonic dystrophy type 2 (P = 0.010), but did not differ with regard to depressed mood, education, motor performance and disease duration (Table 1).

Neuropsychological performance

Neuropsychological performance – group comparison – myotonic dystrophy type 1 and controls
Patients with myotonic dystrophy type 1 had a higher susceptibility to interference compared with our control group. However, the test value was still within the normal range, when compared with the clinical cut-off value for relevant impairment (P = 0.380; Table 2). In contrast, patients with myotonic dystrophy type 1 performed better than controls in the choice reaction time and the recognition task of the verbal memory test. Our control group showed poorer performance in the choice reaction time task in comparison to normative data (P = 0.036). Thus, choice reaction time task results in patients with myotonic dystrophy type 1 did not differ from normative data (P = 0.807). Patients with myotonic dystrophy type 1 performed better in the verbal memory task not only when compared with our control group but also when compared with normative values (P = 0.033; Table 2).

Analysis of increased daytime sleepiness/fatigue showed that our myotonic dystrophy type 1 patient group reached higher scores than controls in all applied scales. However, mean scores above the clinical cut-off of pathological performing were found in 15/22 (68%) patients with myotonic dystrophy type 1 with Krupp’s Fatigue Severity Scale (KFSS; Krupp et al., 1989), in
Table 2  Neuropsychological function, controlled for motor performance, in patients with myotonic dystrophy type 1 and myotonic dystrophy type 2 compared with controls (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Myotonic dystrophy type 1 (n = 22)</th>
<th>Myotonic dystrophy type 2 (n = 22)</th>
<th>Controls (n = 22)</th>
<th>Myotonic dystrophy type 1 versus controls</th>
<th>Myotonic dystrophy type 2 versus controls</th>
<th>Myotonic dystrophy type 1 versus myotonic dystrophy type 2 F-value (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focused attention (c.I.T.S)</td>
<td>19.64 (5.06)</td>
<td>20.55 (5.48)</td>
<td>15.76 (2.77)</td>
<td>3.135 (0.084)*</td>
<td></td>
<td>9.918 (0.003)**</td>
</tr>
<tr>
<td>Interference (c.I.T.I)</td>
<td>27.50 (7.84)</td>
<td>25.82 (5.65)</td>
<td>19.38 (4.71)</td>
<td></td>
<td>6.411 (0.015)**</td>
<td>8.932 (0.005)**</td>
</tr>
<tr>
<td>Psychomotoric speed (TMT A)</td>
<td>33.45 (11.70)</td>
<td>39.00 (16.29)</td>
<td>36.24 (14.29)</td>
<td>2.136 (0.152)</td>
<td></td>
<td>0.280 (0.651)*</td>
</tr>
<tr>
<td>Attention shift, mental flexibility (TMT B)</td>
<td>96.52 (48.75)</td>
<td>90.27 (35.24)</td>
<td>83.52 (32.70)</td>
<td>0.001 (0.970)</td>
<td>0.662 (0.421)*</td>
<td>0.002 (0.961)*</td>
</tr>
<tr>
<td>Naming (Boston Naming)</td>
<td>54.36 (4.09)</td>
<td>56.32 (7.47)</td>
<td>56.67 (4.38)</td>
<td>1.199 (0.280)</td>
<td></td>
<td>2.719 (0.107)</td>
</tr>
<tr>
<td>Phonemic fluency</td>
<td>29.50 (7.74)</td>
<td>29.45 (9.56)</td>
<td>33.57 (9.54)</td>
<td>0.111 (0.918)*</td>
<td>0.261 (0.612)*</td>
<td>0.235 (0.621)*</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>23.77 (5.77)</td>
<td>22.18 (6.34)</td>
<td>24.48 (4.57)</td>
<td>0.204 (0.654)</td>
<td>0.717 (0.402)</td>
<td>1.420 (0.240)</td>
</tr>
<tr>
<td>Visual-spatial / visual-constructive abilities (Blocktest)</td>
<td>22.32 (10.54)</td>
<td>29.95 (7.97)</td>
<td>27.90 (8.01)</td>
<td>0.499 (0.484)*</td>
<td>2.432 (0.127)*</td>
<td>4.321 (0.044)**</td>
</tr>
<tr>
<td>Reaction time (NeurocogFX)</td>
<td>263.82 (55.56)</td>
<td>294.61 (73.85)</td>
<td>258.52 (47.80)</td>
<td>0.001 (0.974)</td>
<td></td>
<td>1.555 (0.220)</td>
</tr>
<tr>
<td>Choice reaction time (NeurocogFX)</td>
<td>98.64 (58.56)</td>
<td>141.86 (60.30)</td>
<td>135.76 (57.85)</td>
<td>9.491 (0.004)**</td>
<td>0.229 (0.635)</td>
<td>6.534 (0.014)*</td>
</tr>
<tr>
<td>Interference (NeurocogFX)</td>
<td>388.91 (57.14)</td>
<td>492.59 (84.34)</td>
<td>412.57 (71.22)</td>
<td>3.528 (0.068)</td>
<td>1.642 (0.207)</td>
<td>13.345 (0.001)**</td>
</tr>
<tr>
<td>Verbal memory-recognition (NeurocogFX)</td>
<td>43.16 (4.18)</td>
<td>36.50 (6.86)</td>
<td>40.88 (2.98)</td>
<td>6.912 (0.012)*</td>
<td>0.051 (0.823)</td>
<td>6.457 (0.015)**</td>
</tr>
<tr>
<td>Figural memory-recognition (NeurocogFX)</td>
<td>5.59 (7.43)</td>
<td>7.68 (8.16)</td>
<td>6.57 (8.53)</td>
<td>0.711 (0.404)*</td>
<td>2.863 (0.056)*</td>
<td>0.072 (0.790)*</td>
</tr>
</tbody>
</table>

*Significant influence of motor performance.

Names of the applied test or test battery for each neuropsychological function are given in brackets. For details regarding the neuropsychological tests, see Supplementary material.

**P < 0.05, ***P < 0.01.

c.I.T.S = subtest (symbol counting) of the Cerebraler Insuffizienztest; c.I.T.I = subtest (response inhibition) of the Cerebraler Insuffizienztest; NeurocogFX = computerised neuropsychological screening test battery; TMT = Trail-Making Test.
dystrophy types 1 and 2 compared with controls (sum of bihemispheric subscors, myotonic dystrophy type 1 \( P < 0.001 \), myotonic dystrophy type 2 \( P = 0.02 \)). Temporal white matter lesions were restricted to patients with myotonic dystrophy type 1. Mild infratentorial white matter lesions (subscore 1) were only found in one control, mild parieto-occipital and unilateral frontal lesions were present in three and two controls, respectively (subscores 1). The remaining controls did not show white matter lesions Table 5). Both patient groups did not differ with regard to total white matter lesions scores or subscores.

Voxel-based morphometry

Compared with controls, we found grey matter alterations in patients with myotonic dystrophy type 1 in various cortical regions of both hemispheres, mainly located in frontal and parietal regions, whereas temporal lobes were spared. Most notably, pre- and postcentral gyrus and the supplementary motor area were bilaterally affected. Additional subcortical grey matter alteration was detected in the right posterior thalamus and in the most anterior part of the right putamen.

White matter decrease was more pronounced than grey matter decrease. It affected the entire corpus callosum, both fornices, cingulum bundle and white matter in every lobe. Further white matter decrease was located at brainstem level (pons), along middle cerebellar peduncles and in cerebellar white matter (Supplementary Table 1; Fig. 1).

In contrast to myotonic dystrophy type 1, no grey matter decrease was detected in patients with myotonic dystrophy type 2 compared with controls. White matter decrease, however, was pronounced and located along the entire corpus callosum and in every lobe, although the regions were less confluent than in myotonic dystrophy type 1. Further, white matter loss was present at brainstem level (pons), along middle cerebellar peduncles and in cerebellar white matter (Supplementary Table 2; Fig. 1).

### Diffusion tensor imaging

#### Diffusion tensor imaging – group comparison – myotonic dystrophy type 1 and controls

Compared with controls, in patients with myotonic dystrophy type 1 we detected ubiquitous fractional anisotropy reduction in association fibres: bilateral superior and inferior longitudinal fascicles, inferior fronto-occipital fascicles and uncinate fascicles, both fornices, cingulum bundles and hippocampal parts of the posterior cingulum bundle. The corpus callosum as main commissural tract was affected in all parts, sparing only parts of the splenium. In addition, projection fibres as internal capsules (anterior/posterior limbs, retrolenticular parts) and external capsules, both corticospinal tracts at the level of internal capsules and brainstem at pontine level were affected (Fig. 2, Supplementary Table 3).

The areas of increased radial diffusivity and mean diffusivity closely mirrored the areas of fractional anisotropy reduction. Compared with fractional anisotropy reduction, some regions were even more continuously affected and reached more to the outlying border of affected fibre tracts. An increase of axial diffusivity was found in parts of regions with fractional anisotropy reduction (Fig. 3).

#### Diffusion tensor imaging – group comparison – myotonic dystrophy type 2 and controls

Compared with controls, in patients with myotonic dystrophy type 2 we detected prominent fractional anisotropy reduction in association fibres: bilateral superior longitudinal fascicles, inferior longitudinal fascicles, inferior fronto-occipital fascicles, uncinate fascicles, cingulum bundles and fornices. The corpus callosum was mainly affected in its anterior parts and more severely affected on the left side. Anterior limbs of both internal capsules (left > right) and both external capsules were affected as projection fibres (Fig. 2, Supplementary Table 3).

The areas of increased radial diffusivity mirrored those with fractional anisotropy reduction, but there were additional small significant areas with increased axial diffusivity in some fibre tracts. There was little overlap between fractional anisotropy reduction and increased axial diffusivity in areas of significance. An increase in mean diffusivity was again found in similar regions as fractional anisotropy reduction, although not all regions with fractional anisotropy reduction showed an increase of mean diffusivity (Fig. 3).
Table 4 Pearson product–moment correlation coefficient for correlations (P-values are given in brackets) between neuropsychological tests and fatigue/sleepiness scales with age, disease duration, motor performance and BDI score

<table>
<thead>
<tr>
<th>Function</th>
<th>Myotonic dystrophy type 1</th>
<th>Myotonic dystrophy type 2</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 0.14 (0.534)</td>
<td>Age 0.07 (0.768)</td>
<td>0.33 (0.144)</td>
</tr>
<tr>
<td></td>
<td>Disease duration 0.02 (0.938)</td>
<td>Disease duration –0.29 (0.195)</td>
<td>0.72 (0.758)</td>
</tr>
<tr>
<td></td>
<td>Motor performance –0.43 (0.046)*</td>
<td>Motor performance –0.09 (0.682)</td>
<td>0.04 (0.866)</td>
</tr>
<tr>
<td></td>
<td>Depressed mood –0.25 (0.912)</td>
<td>Depressed mood 0.18 (0.444)</td>
<td>0.04 (0.866)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interference</td>
<td>Choice reaction time</td>
<td>Verbal memory-rec.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Neuro-Cog FX)</td>
<td>(Neuro-Cog FX)</td>
</tr>
<tr>
<td></td>
<td>0.44 (0.040)*</td>
<td>0.55 (0.007)**</td>
<td>–0.65 (0.001)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–0.30 (0.169)</td>
<td>–0.04 (0.877)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>–0.42 (0.053)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>–0.27 (0.233)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Choice reaction time</td>
<td>Depressed mood</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>(Neuro-Cog FX)</td>
<td>(BDI)</td>
<td>(KFSS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–0.14 (0.536)</td>
<td>0.91 (0.687)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–0.23 (0.301)</td>
<td>0.46 (0.031)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.61 (0.003)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.89 (0.000)**</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Choice reaction time</td>
<td>Fatigue</td>
<td>Daytime sleepiness</td>
</tr>
<tr>
<td></td>
<td>(Neuro-Cog FX)</td>
<td>(KFSS)</td>
<td>(DSS)</td>
</tr>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>Choice reaction time</td>
<td>Verbal memory-rec.</td>
<td>Sleep quality</td>
</tr>
<tr>
<td></td>
<td>(Neuro-Cog FX)</td>
<td>(Neuro-Cog FX)</td>
<td>(PSQI)</td>
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</tbody>
</table>

Names of the applied test or test battery for each neuropsychological function are given in brackets. For details regarding the neuropsychological tests, see Supplementary material.

*Significant differences (P < 0.05), **Significant differences (P < 0.01), ***Significant differences (P < 0.001).

c.i.T.S = subtest (symbol counting) of the Cerebral Insuffizienztest; c.i.T.I. = subtest (response inhibition) of the Cerebral Insuffizienztest; DSS = Daytime Sleepiness Scale; NeurocogFX = computerised neuropsychological screening test battery.

This region showed further correlations with age, disease duration, and motor performance. In contrast, no significant correlations were found with clinical parameters.

In clinical parameters, correlation analyses with ARWMC = age-related white matter change score.

Table 5 White matter hyperintensities rated according the ARWMC scale in patients with myotonic dystrophy types 1 and 2 and control subjects (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Myotonic dystrophy type 1</th>
<th>Myotonic dystrophy type 2</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total score</td>
<td></td>
<td>Patient score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARWMC (age-related white matter change score)</td>
</tr>
<tr>
<td></td>
<td>1.82 ± 2.79</td>
<td>0.69 ± 0.66</td>
<td>0.26 ± 0.62</td>
</tr>
<tr>
<td></td>
<td>(0.32)</td>
<td>(0.32)</td>
<td>(0.32)</td>
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<tr>
<td></td>
<td>(0.32)</td>
<td>(0.32)</td>
<td>(0.32)</td>
</tr>
</tbody>
</table>
Figure 1  Neuroimaging results of the brain (VBM, group comparisons). Displayed results of VBM analyses are based on a threshold of $P_{\text{false discovery rate}} < 0.05$ at voxel-level with an extended cluster threshold of 10 voxels. The coordinates refer to the MNI reference space. (A) Grey matter decrease in patients with myotonic dystrophy type 1 compared with controls. (B) White matter decrease in patients with myotonic dystrophy type 1 compared with controls. (C) Grey matter decrease in patients with myotonic dystrophy type 2 compared with controls (no clusters detected). (D) White matter decrease in patients with myotonic dystrophy type 2 compared with controls.
neuropsychological tests (interference, choice reaction time, verbal memory test) gave mixed results with marginal and inconsistent associations that involved only few voxels (data not shown).

**Diffusion tensor imaging – correlation analyses with clinical and neuropsychological data – myotonic dystrophy type 2**

Lower fractional anisotropy values occurred with higher age, longer disease duration and poorer motor performance in various brain regions, especially association fibres, cingulum bundles, fornices, anterior limb of internal capsules, corpus callosum and right external capsule. With respect to higher age and longer disease duration, we found more frontally accentuated reduced fractional anisotropy values compared with myotonic dystrophy type 1, affecting comparable but not identical fibre parts. Further, the changes were more pronounced with age than with disease duration. Correlation analyses of fractional anisotropy values with motor performance showed regions in the right external capsule, while in contrast to myotonic dystrophy type 1 no associations with posterior limbs of internal capsules were present. In contrast to myotonic dystrophy type 1, lower fractional anisotropy values were associated with a more depressed mood and increased fatigue in myotonic dystrophy type 2 (Fig. 4). Further details of fractional anisotropy correlation analyses with clinical parameters are given in Supplementary Table 4.

Correlation analyses with neuropsychological tests (interference, focused attention) did not show significant results (data not shown).

**Discussion**

We present a comprehensive study of brain structure and function in a comparably large series of patients with myotonic dystrophy types 1 and 2. Our neuroimaging findings confirmed the major hypotheses of our study: we found severe white matter effects in patients with myotonic dystrophy type 1, more than in patients with myotonic dystrophy type 2, which extensively exceeded grey matter involvement in both disorders. We applied DTI based on diffusion MRI, which is a suitable method for white matter evaluation. Even though VBM is not the method of choice for white
matter evaluation, our DTI results were strongly supported by VBM analyses.

White matter effects were found throughout the whole brain in myotonic dystrophy types 1 and 2, affecting association fibres, commissural fibres (mainly corpus callosum), and projection fibres in the brainstem, internal and external capsules, the latter connecting prefrontal and temporal cortical areas with the striatum. Thalamocortical pathways (e.g. anterior thalamic radiation) and prefrontal connections are represented in anterior limbs of internal capsules, which were affected in myotonic dystrophy types 1 and 2. Interestingly, anterior limb lesions had previously been described in the context of behavioural problems and cognitive dysfunction (Mamah et al., 2010). In contrast, central motor pathways (e.g. corticospinal tracts located in posterior limbs of internal capsules) were exclusively affected in myotonic dystrophy type 1.

Our data on white matter in adult patients with myotonic dystrophy type 1 give evidence that callosal body affection is not restricted to congenital myotonic dystrophy type 1. Current results confirm callosal body affection in patients with myotonic dystrophy type 2 as previously demonstrated by our VBM and surface-based morphometry analyses (Minnerop et al., 2008), and demonstrate a predominant affection of anterior callosal fibres connecting frontal lobes in myotonic dystrophy type 2. We further found degradation of major pathways of the limbic system (e.g. fornix, cingulum bundle) in patients with myotonic dystrophy type 1, more than in patients with myotonic dystrophy type 2. This finding could be associated with behavioural abnormalities and emotional disturbances in myotonic dystrophies. This question should be addressed in future studies investigating personality traits in both disorders.

In the current patient series, cortical grey matter affection was only found in myotonic dystrophy type 1. Cortical grey matter loss was located in frontal and parietal regions, whereas subcortical grey matter loss was detected in thalamic and basal ganglia structures. This is in line with the literature, describing widespread cortical and subcortical grey matter alterations in myotonic dystrophy type 1 (Antonini et al., 2004; Weber et al., 2010). Previous analyses, including one of our own studies, also found grey matter changes in myotonic dystrophy type 2 (Minnerop et al., 2008; Weber et al., 2010). This discrepancy to our present data may be attributed to differences in sample size as earlier studies investigated smaller patient cohorts.
Figure 4  Neuroimaging results of the brain (DTI, correlation analyses between white matter affection (fractional anisotropy values) and clinical parameters). Correlation analyses in myotonic dystrophy type 1 (A–G) and myotonic dystrophy type 2 (H–L). Displayed results of Tract-based spatial statistics analyses of fractional anisotropy values are based on a corrected threshold of $P_{\text{threshold-free cluster enhancement}} < 0.05$. Mean tract-based spatial statistics tract skeleton is overlaid on the mean fractional anisotropy image (display threshold of 0.1).

(continued)
Though our patients with myotonic dystrophy type 2 were older than our patients with myotonic dystrophy type 1, the myotonic dystrophy type 2 cohort encompassed rather ‘young’ subjects regarding the common disease manifestation at higher ages. With respect to the clinical course of myotonic dystrophy type 2, an older cohort with longer disease durations might have been more appropriate. Less pronounced cerebral grey and white matter affection in patients with myotonic dystrophy type 2 compared with patients with myotonic dystrophy type 1 might be partially explained by this fact.

White matter lesions and brain atrophy are well known in myotonic dystrophy types 1 and 2, but current data suggest that the underlying pathology seems to (i) affect white matter much more than grey matter and (ii) affect white matter far beyond circumscribed white matter lesions visible on T2-weighted MRIs. These findings link myotonic dystrophies to the growing group of brain disconnection disorders. The neuropathological background of white matter changes in myotonic dystrophies is still not fully understood. Neuropathological findings in myotonic dystrophy type 1 brains include abnormalities like intracytoplasmic inclusions in thalamus, striatum, cerebral cortex and brainstem (Rosman and Kakulas, 1966; Wniewiaski et al., 1975; Ono et al., 1987). Further studies in myotonic dystrophy type 1 and myotonic dystrophy type 2 brains found evidence of neurofibrillary degeneration with intracellular aggregation of microtubule-associated tau protein (Vermersch et al., 1996; Sergeant et al., 2001; Maurage et al., 2005; Itoh et al., 2010). Most changes are located in neurons; however, white matter alterations including disordered arrangement of myelin sheaths and axons have been described (Abe et al., 1994; Ogata et al., 1998; Itoh et al., 2010). It is widely accepted that the integrity of axonal membranes and myelin sheaths are the main biological causes of anisotropy in DTI (Beaulieu, 2002). Reduced fractional anisotropy values in the current study were primarily linked with an increase of radial diffusivity. Increased radial diffusivity can be either caused by reduced myelin sheaths/defect axonal membranes or as a consequence of neuronal cell loss with Wallerian degeneration. A likely explanation for our finding of an additional increase of axial diffusivity (theoretically leading to an increase of fractional anisotropy) in some areas with fractional anisotropy reduction is increased water content in the context of atrophy as described in the ‘healthy’ ageing brain (Moseley, 2002). This phenomenon leads to an increase of both radial more than axial diffusivity, finally resulting in a decrease of fractional anisotropy. The changes of diffusivity in white matter fibre tracts were more prominent in myotonic dystrophy type 1 than type 2. This is possibly a consequence of genetic differences with a disease-specific pathomechanism of tissue destruction, which however results in abnormal increases of water diffusion perpendicular to axons in both disorders. We have to consider that reduced fractional anisotropy values in genetically determined disorders might not reflect ongoing destructive processes, but instead a developmental defect with disturbed assembly of myelin and/or axonal membranes. The widespread changes in myotonic dystrophy type 1 may point towards a generalized white matter defect. However, the correlation of lower fractional anisotropy values with longer disease duration and higher age in myotonic dystrophy type 1 and myotonic dystrophy type 2 strongly argue for an ongoing destruction of myelin and/or axonal loss over time. The fact that white matter changes by far dominated the extent of grey matter changes in myotonic dystrophy types 1 and 2 might further argue against Wallerian degeneration as the major cause of white matter alterations as formerly postulated (Ota et al., 2006).

**Relation of white matter integrity and motor function**

Impaired motor function due to muscle affection is one of the most characteristic symptoms in myotonic dystrophy types 1 and 2. However, subclinical dysfunction of the central motor system had been described in myotonic dystrophy type 1 (Oliveri et al., 1997; Mitsuoka et al., 2003). We found reduced fractional anisotropy values in posterior limbs of internal capsules (corticospinal tract) in myotonic dystrophy type 1, not in myotonic dystrophy type 2, which correlated with motor performance in a simple motor task (bimanual pegboard). In the group comparison, we found reduced fractional anisotropy values along external capsules in patients with myotonic dystrophy types 1 and 2, correlating with the Muscular Impairment Rating Scale score (measuring muscular impairment) in myotonic dystrophy type 1 and motor performance in myotonic dystrophy type 1 and type 2. The external capsule contains corticostriatal projection fibres connecting prefrontal and temporal areas with basal ganglia, known to play a major role in motion planning and execution. A recent functional MRI study in myotonic dystrophy type 1 showed activation patterns in central motor system areas that resembled those in healthy older subjects (Caramia et al., 2010). Taken together, these findings give evidence of impaired central motor functioning in myotonic dystrophies, potentially reflecting an accelerated or increased ageing process.

**Neuropsychological performance**

Neuropsychological deficits, especially of executive and visuospatial functions, have been frequently described in myotonic dystrophy types 1 and 2 (Meola et al., 1999, 2003; Gaul et al., 2006; Meola and Sansone, 2007; Romeo et al., 2010). However, most
impaired frontal lobe function is a predominant finding in myo-
frontal lobe dysfunction in both myotonic dystrophy types 1 and
also showed impaired focused attention, pointing towards
also significantly present in myotonic dystrophy type 2, which
psychological deficit in our myotonic dystrophy type 1 series and
Increased liability for interference was the only significant neuro-
tical reasons, we used (i) the German
by the study protocol (combined neuroimaging study). For prac-
ted for use in patients with myotonic dystrophy worldwide.
Accordingly, the most sensitive and reliable, best validated, and
most applicable tests are expected to be selected in the near
future. Our neuropsychological test selection was a compromise
resulting from our experience in patients with neurological/neuro-
degenerative disorders and the time constraints that were dictated
by the study protocol (combined neuroimaging study). For prac-
tical reasons, we used (i) the German NeuroCogFX, which is
validated in a variety of neurological disorders and has also been
applied to other trinucleotide repeat disorders (Fliessbach et al.,
2006; Hoppe et al., 2009; Klinke et al., 2010) and (ii) the
Cerebraler Insuffizientest (Lehrl and Fischer, 1997), which
assesses attention and interference in a reliable and fast way com-
pared with other frontal lobe function tests. However, some of the
applied tests had not previously been systematically used in myo-
tonic dystrophies. Thus, the selection of the neuropsychological
test battery might have additionally influenced the neuropsycho-
logical profiling of our patients.

Relation of white matter integrity and
depression

Depressive symptoms are well known in myotonic dystrophy types
1 and 2, but do not seem to be a prominent feature if DSM-IV
(Diagnostic and Statistical Manual of Mental Disorders) criteria are
applied (Meola and Sansone, 2007). Using the self-rating ques-
questionnaire BDI, Winblad et al. (2010) found signs of mostly mild
depression in 32% of examined patients with myotonic dystrophy
type 1, which is identical to our findings in myotonic dystrophy
type 1 (32%) and type 2 (38%). However, it is still a matter of
debate if depression might be a consequence of structural brain
damage or rather a reactive adjustment disorder. We therefore
investigated the interaction between fractional anisotropy reduc-
tion and BDI scores and found higher BDI scores associated with
higher fractional anisotropy values in myotonic dystrophy type 1,
whereas higher BDI scores were associated with lower fractional
anisotropy values in myotonic dystrophy type 2. Regression ana-
lyses in myotonic dystrophy type 1 and type 2 revealed a decline of
fractional anisotropy with increasing age and disease duration.
Thus, our results implicate that depressed mood in myotonic dys-
trophy type 1 might be more pronounced in earlier disease stages,
whereas depression is more likely to be found in later disease stages
of myotonic dystrophy type 2. Our results are supported by recent data of Winblad et al. (2010): the authors found less
depressive symptoms in patients with myotonic dystrophy type 1
with a longer disease duration and presence of white matter
lesions, whereas patients with myotonic dystrophy type 1 without
white matter lesions had more depressive symptoms (Winblad
et al., 2010). If depressed mood was a consequence of structural
brain affection, a continuous worsening of depression would
be expected as myotonic dystrophy types 1 and 2 progress. Our
results indicate that depression might be a reactive adjustment
disorder rather than a consequence of structural brain damage
in myotonic dystrophies. Myotonic dystrophy type 1 is more severe
in general and leads to a more serious impairment in earlier life
than myotonic dystrophy type 2. Therefore, patients with myotonic
dystrophy type 1 are more likely to notice early limitations in
everyday activities and develop reactive depression. As disease
progresses, these patients may develop efficient coping strategies
or may be less able to perceive their limitations due to cognitive
deficits or personality changes. Since we found only minor neu-
ropsychological deficits, the so called ‘lack of awareness’ may
explain the presence of a less depressed mood in advanced disease
stages (Meola and Sansone, 2007; Winblad et al., 2010). This
condition has previously been linked to localized brain lesions in other disorders, affecting regions (prefrontal cortex, frontal and parietotemporal areas, thalamus) that also show structural abnormalities in myotonic dystrophy type 1 (Orfei et al., 2008; Winblad et al., 2010). Myotonic dystrophy type 2 is usually less severe, and patients may not notice serious limitations in everyday life in early disease stages. Symptoms worsen over time and may cause depression in advanced disease stages. However, we did not find direct correlations between BDI scores and age or disease duration in myotonic dystrophy type 1 or 2. The use of additional depression scores would have been favourable, though was not practicable in the present comprehensive study setting, which took several hours and required careful consideration of patients’ psychophysical limits as well as time constraints.

**Relation of white matter integrity and increased daytime sleepiness/fatigue**

Increased daytime sleepiness and fatigue are among the most frequent non-muscular symptoms in patients with myotonic dystrophy type 1 and type 2 (Hilton-Jones, 1997; van der Werf et al., 2003; Meola and Sansone, 2007; Laberge et al., 2009a, b; Tieleman et al., 2010). Weak oropharyngeal and respiratory muscles leading to obstructive sleep apnoea and alveolar hypventilation have been regarded as causative factors of daytime sleepiness. However, there is increasing evidence that tiredness primarily results from CNS dysfunction rather than progressive respiratory weakness (van der Mech et al., 1994; Park and Radtke, 1995; Rubinsztein et al., 1998; Laberge et al., 2009a, b; Romigi et al., 2011; Yu et al., 2011). An association with the hypocrein neurotransmission system had been suggested. However, data regarding the role of hypocretin-1, a hypothalamic neuropeptide essential in the regulation of the sleep/wakefulness cycle and vigilance, are still controversial (Martinez-Rodriguez et al., 2003; Ciafaloni et al., 2008).

Fatigue, equivocally defined as a lack of energy and feeling of exhaustion (Shen et al., 2006), is a prominent and common complaint in myotonic dystrophy type 1 (60–80%; Kalkman et al., 2005; Meola and Sansone, 2007; Laberge et al., 2009b; Tieleman et al., 2010). The prevalence of fatigue in myotonic dystrophy type 2 has been investigated only very recently, finding a similar result of 66% (Tieleman et al., 2010). These data are in accordance with our findings, showing a prevalence of 68–70% fatigue in patients with myotonic dystrophy types 1 and 2. While our patients with myotonic dystrophy type 1 differed from controls in all sleepiness and fatigue scales, patients with myotonic dystrophy type 2 differed from controls only in PSQI and KFSS scores, not in daytime sleepiness scales. This again is in line with findings of Tieleman et al. (2010). Subjective sleep quality, as measured by the total PSQI score, was impaired in ~40% of both patient groups, which might be an indicator of a disturbed sleep/awakening cycle in myotonic dystrophy types 1 and 2 and should be further examined by polysomnographic studies.

We performed correlation analyses to evaluate the relation between fatigue (KFSS score) and white matter integrity (fractional anisotropy values). Similar to results of regression analyses with BDI scores, we found that higher fractional anisotropy values were associated with more pronounced fatigue in myotonic dystrophy type 1. In contrast, lower fractional anisotropy values were associated with more pronounced fatigue in myotonic dystrophy type 2. In contrast to previous findings, anterior corpus callosum integrity did not correlate with fatigue in our study (Giubilei et al., 1999).

Damage to the reticular activating system of the upper brainstem and/or to its cortical projections has already been discussed as related to the chronic fatigue syndrome (Dickinson, 1997). Morphological brainstem changes in myotonic dystrophy type 1 include neurofibrillary tangles, Marinesco bodies, as well as a decrease of serotonergic neurons in raphe nuclei and catecholaminergic neurons in the medullary reticular formation (Ono et al., 1987, 1998a, b; Oyamada et al., 2006). Interestingly, sleep disturbances and apathy were more frequent in patients with myotonic dystrophy type 1 with fewer neurofibrillary tangles (Oyamada et al., 2006). We comparably depicted less fatigue with more pronounced brainstem affection in patients with myotonic dystrophy type 1. Thus, myotonic dystrophy type 1 specific brainstem changes might prevent the feeling of fatigue or again might result in a lack of self-awareness.

Laberge et al. (2009b) found higher depression scores, more muscular impairment, and higher number of CTG repeats in patients with myotonic dystrophy type 1 with fatigue and/or increased sleepiness. This in accordance with our results in myotonic dystrophy type 1, as we found higher KFSS scores correlating with both poorer motor performance and higher BDI scores. In contrast, we did not find a correlation of KFSS with BDI scores in myotonic dystrophy type 2, whereas higher KFSS scores correlated with poorer motor performance similar to myotonic dystrophy type 1 and to controls.

Thus, depressed mood and fatigue were closely related at least in myotonic dystrophy type 1. BDI and KFSS may overlap with regard to the target symptoms, and some questions of the BDI are known to target on symptoms of sleepiness and fatigue. In myotonic dystrophy type 2, we found similar directed correlations of fractional anisotropy values, BDI and KFSS scores. However, we did not find BDI and KFSS scores correlating with each other as shown in myotonic dystrophy type 1. Thus, one might conclude that the applied questionnaires are measuring partially overlapping, but not entirely identical conditions.

Polysomnographic studies as well as the use of further fatigue, anxiety and apathy scales like the Checklist Individual Strength or the Hospital Anxiety and Depression Scale would have been of interest but were not applicable in the current study setting. However, the present data warrant further investigations in the near future.

**Relation of white matter integrity and age, disease duration and CTG repeat size**

The pattern of affected fibre tracts in correlation analyses with age and disease duration was identical in our myotonic dystrophy type...
Premature ageing has been discussed in myotonic dystrophy and is generally found to be more serious morphologically than during normal ageing. Furthermore, age-specific translational dysfunctions have been described in myotonic dystrophy type 2 and might not correlate with repeat lengths in brain and cerebral tissue. Moreover, repeat sizes may increase throughout life even in post-mitotic tissues, which suggests that repeat lengths in blood and much larger expansions in heart or skeletal muscle tissue. Repeat sizes may increase throughout life even in post-mitotic tissues, which suggests that repeat lengths in blood might not correlate with repeat lengths in brain and cerebral affection. Nevertheless, a variety of neuroimaging studies did show more serious morphological cerebral changes with larger repeat expansions in adult patients (Ota et al., 2006; Romeo et al., 2010). Our present findings equally showed that larger CTG repeat sizes were associated with more severe white matter affection in several brain regions. Remarkably, the pattern of fibre tract degradation that was associated with larger CTG repeats was similar to the pattern that was associated with higher age and longer disease duration. These findings again may indicate that the effects of the disease itself on white matter structure resembles the effects of ageing in myotonic dystrophy type 1. Specific brain regions might be particularly susceptible to the disease effects that are reflected by CTG repeat lengths and disease duration.

Altogether, our data suggest that white matter affection is progressive over time in myotonic dystrophies. Despite this tempting speculation, cross-sectional data and correlation analyses, as obtained in our study, do not sufficiently allow analyses of the age- and disease duration-related impact on brain morphology in myotonic dystrophy types 1 and 2. Longitudinal MRI studies investigating the progress of grey and white matter changes over time and its role in clinical deterioration in both types of myotonic dystrophies are strongly required to address these issues appropriately in the future.

Acknowledgements

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Supplementary material

Supplementary material is available at Brain online.

References


