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Neurology 2010;74;1108-1117; originally published online Mar 10, 2010;
DOI: 10.1212/WNL.0b013e3181d8c35f

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ABSTRACT

Objective: Myotonic dystrophy type 1 and 2 (DM1/DM2) are multisystemic diseases with common cognitive deficits beside the cardinal muscular symptoms. We performed a comprehensive analysis of cerebral abnormalities to compare the neuropsychological defects with findings in different imaging methods in the same cohort of patients.

Methods: Neuropsychological investigations, structural cerebral MRI including brain parenchymal fraction (BPF) and voxel-based morphometry (VBM), and ^{18}F-deoxy-glucose PET (FDG-PET) were performed in patients (20 DM1 and 9 DM2) and matched healthy controls, and analyzed using statistical parametric mapping (SPM2).

Results: DM1 and DM2 patients showed typical neuropsychological deficits with a pronounced impairment of nonverbal episodic memory. Both patient groups showed a reduction of the global gray matter (measured by BPF), which could be localized to the frontal and parietal lobes by VBM. Interestingly, VBM revealed a bilateral hippocampal volume reduction that was correlated specifically to both a clinical score and episodic memory deficits. VBM also revealed a pronounced change of thalamic gray matter. White matter lesions were found in >50% of patients and their extent was correlated to psychomotor speed. FDG-PET revealed a frontotemporal hypometabolism, independent of the decrease in cortical gray matter. All abnormalities were similar in both patient groups but more pronounced for DM1.

Conclusions: Our results suggest that 1) some of the characteristic cognitive deficits of these patients are linked to specific structural cerebral changes, 2) decreases in gray matter and metabolism are independent processes, and 3) the widespread brain abnormalities are more pronounced in DM1. *Neurology*® 2010;74:1108–1117

GLOSSARY

BPF = brain parenchymal fraction; **C** = controls; **cMRI** = cranial MRI; **DM1** = myotonic dystrophy type 1; **DM2** = myotonic dystrophy type 2; **FDG-PET** = ^{18}F-deoxy-glucose positron emission tomography; **FLAIR** = fluid-attenuated inversion recovery; **GA** = divided alertness test; **MMSE** = Mini-Mental State Examination; **ROF** = Rey-Osterrieth figure copy (I) and recall (II); **SL** = slice thickness; **SPM** = statistical parametric mapping; **TE** = echo time; **TMT** = Trail Making Test; **TR** = repetition time; **VBM** = voxel-based morphometry; **WML** = white matter lesion; **WMS** = Wechsler Memory Scale; **WST** = vocabulary test.

Myotonic dystrophy 1 (DM1) and 2 (DM2) are multisystemic diseases.[1-6] Cognitive deficits are found in a high percentage of patients. In DM1, cognitive deficits have been observed in 24%–75%[7-9] and are characterized by defective visuospatial/constructional abilities, attention, and verbal memory up to severe mental decline.[10] In addition, somatic abnormalities have been described: microcephaly or thickening of the calvarium,[11] white matter lesions (WML) and atrophy,[10] decreased cerebral glucose metabolism,[12-14] hypoperfusion in the fronto-temporo-parietal cortex,[15] reduced cerebral blood flow,[8,15] and changes in cerebral metabolites.[16] Corre-

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Supplemental data at www.neurology.org

e-Pub ahead of print on March 10, 2010, at www.neurology.org.

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Study funding: Supported by the University of Ulm (Zentrum Angewandte Klinische Forschung, project P.603).

Disclosure: Author disclosures are provided at the end of the article.

lation analyses between neuropsychological deficits and brain abnormalities revealed inconsistent results in DM1. The extent of WML and brain atrophy were correlated to the Mini-Mental State Examination (MMSE)[17] and frontotemporal hypoperfusion to IQ.[15] Other studies could not confirm these findings.[18-20]

Cognitive deficits in DM2 are similar to those observed in DM1.[8,21] WML, atrophy, cerebral hypoperfusion, and changes in cerebral metabolites have also been described.[8,16,22,23] A clear correlation of WML and brain atrophy to the neuropsychological deficits could not be detected.[8] Brain glucose utilization has only been studied in 1 patient with DM2.[24]

In our study, we integrate the characterization of structural and functional aspects of brain abnormalities in the same cohort of patients compared to matched controls. We used 1) a neuropsychological test battery, 2) cranial MRI including optimized voxel-based morphometry, calculation of brain parenchymal fraction, and quantification of WML, 3) ^{18}F-deoxy-glucose PET (FDG-PET) including partial volume correction for cortical atrophy, and 4) extensive correlation studies and data analysis with statistical parametric mapping (SPM).

METHODS

Standard protocol approvals, registrations, and patient consents. Approval for all procedures in this study was obtained from the Ethical Committee of the University Clinic Ulm and written informed consent was received from all participants.

Patients. DM families from the collection of patients of the Institutes of Applied Physiology and Human Genetics of the University of Ulm, Germany, were contacted by phone or open letter explaining the study. Exclusion criteria were hypertension, nicotine use, diabetes, hyperlipidemia, adipositas, alcohol abuse, atrial fibrillation, coronary artery disease, peripheral vascular disease, previous myocardial or brain infarction or TIA, vascular dementia, pregnancy, planned pregnancy, or breastfeeding. Patients with a severe neurologic deficit and early disease onset or a congenital form of DM1 were also excluded, since severely affected patients would not have been able to perform all investigations and this preselection had the additional advantage to examine a relatively homogeneous population of moderately affected patients. Twenty German DM1 patients from 18 unrelated families and 9 German DM2 patients from 4 unrelated families were included in the study. The diagnosis of DM1 and DM2 was based on clinical examination, electromyography, and the underlying genetic defects: the analysis of the CTG repeat on chromosome 19q13 for DM1 and the CCTG repeat expansion on chromosome 3q in DM2 patients by standard techniques.[6,25] The muscle impairment was measured by using a modified form of the muscular disability rate based on a 5-point scale (Muscular Disability Rating Scale[26]; see appendix e-1 on the *Neurology*® Web site at www.neurology.org).

We developed a clinical score for the general clinical status of the patients. In DM1 patients, this score was calculated as the sum of the current age (0 for ≤50 years, 1 for >50 and <60 years, 2 for ≥60 years), the length of the CTG repeat (number of CTGs divided by 300), and the disease duration (disease duration in years divided by 10). For DM2 patients, we only added the values obtained for age and disease duration.

Controls. A core group of 13 healthy controls (C) underwent all investigations, i.e., a clinical and neuropsychological investigation, cranial MRI (cMRI), and FDG-PET. To increase the number of controls for each of these investigations and optimally match them for age, gender, and education, we recruited additional cohorts of healthy individuals serving as controls: 1) for the neuropsychological investigations 20 additional controls were separately recruited for comparison with DM1 and 18 for DM2 patients, 2) for cMRI (20 for DM1 and 18 for DM2), and 3) for FDG-PET (18 for DM1 and 16 for DM2). Table e-1A provides an overview of the different control cohorts. The use of the different control groups for respective data evaluation is specified in the Results and figure legends.

Neuropsychological investigations. Cognitive function was assessed in all patients and the respective control groups with a neuropsychological test battery taking approximately 90 minutes to complete. The examinations were performed in a quiet room by trained investigators. A detailed description of the test battery is provided in appendix e-1.

MRI of the brain. MRI scanning was performed in all patients and respective controls on a 1.5-Tesla scanner (Magnetom Vision, Siemens, Erlangen, Germany) with a standard head coil. The scanning protocol included an axial T1-weighted (repetition time [TR] 532 msec, echo time [TE] 17 msec, slice thickness [SL] 5 mm), a T2-weighted (TR 2,475 msec, TE 102 msec, SL 5 mm), and a fluid-attenuated inversion recovery (FLAIR) sequence (TR 9,000 msec, TE 110 msec, SL 5 mm).

WML were considered as present in cases of hyperintense lesions on FLAIR and T2-weighted images. WML were defined as periventricular up to a distance of 3 mm from the ventricle, others as subcortical. WML were rated semiquantitatively as 0 (not present), 1 (small, 1–3 mm), 2 (medium, 3–10 mm), or 3 (large confluent, more than 10 mm), separately in the frontal, temporal, and parieto-occipital lobes, and in the centrum semiovale/periventricular region. The score for each lobe/region was assessed for subcortical and periventricular WML and the values added to yield one global score for WML (minimum 0, maximum 48 points).

In 14 DM1 patients, 9 DM2 patients, and respective controls, a 3-dimensional T1-weighted magnetization-prepared rapid-acquisition gradient echo sequence (TR 9.7 msec, TE 3.93 msec, flip angle 15°, matrix size 256 × 256 mm^2, voxel size 1 × 1 × 1 mm) was acquired. The 3-dimensional MRI data were analyzed using the optimized voxel-based morphometry protocol (VBM)[27] using statistical parametric mapping (SPM2). The procedure was made available by Christian Gaser from the University of Jena as the VBM Toolbox for SPM2, version 1.02. A detailed description of the analysis is provided in appendix e-1. Correlation analysis was only performed using

Table 1 Demographic, clinical, and neuropsychological data for DM1 and DM2 patients vs controls[a]

	DM1	DM1 controls	*p* Values for DM1 vs controls	DM2	DM2 controls	*p* Values for DM2 vs controls
No. (F/M)	20 (9/11)	20 (8/12)	—	9 (6/3)	18 (12/6)	—
Age, y	37.2 ± 14.2	40.3 ± 12.5	NS	53.4 ± 10.9	50.8 ± 10.2	NS
Education, y	10.2 ± 1.8	10.8 ± 1.7	NS	11.6 ± 2.0	10.9 ± 1.8	NS
Muscular Disability Rating Scale	3.1 ± 0.8	—	—	2.4 ± 1.7	—	—
Disease duration, y	16.0 ± 9.6	—	—	23.0 ± 15.0	—	—
Mini-Mental State Examination	28.2 ± 1.9	29.5 ± 0.8	0.03[b]	28.9 ± 1.4	29.4 ± 0.8	NS
SANFT	11.6 ± 5.0	14.8 ± 0.6	NS	13.7 ± 2.2	14.8 ± 0.4	0.03[b]
Vocabulary test	23.8 ± 6.6	30.4 ± 4.5	0.004	32.5 ± 2.4	31.9 ± 3.6	NS
Clock	1.6 ± 0.8	1.1 ± 0.2	0.03[b]	1.4 ± 0.5	1.1 ± 0.2	0.01[b]
Rey-Osterrieth figure copy	33.3 ± 4.5	35.7 ± 0.9	0.02[b]	33.2 ± 5.3	35.6 ± 1.1	NS
Rey-Osterrieth figure recall	19.7 ± 9.0	25.4 ± 5.1	0.03[b]	14.8 ± 7.7	24.4 ± 5.1	0.001[b]
Wechsler Memory Scale	39.9 ± 17.3	64.5 ± 15.7	0.0001[b]	45.1 ± 14.8	59.4 ± 15.8	0.04[b]
Corsi block span	11.4 ± 4.1	15.0 ± 3.8	0.01[b]	13.0 ± 3.6	13.8 ± 3.0	NS
Wisconsin Card Sorting Test	3.9 ± 2.3	3.9 ± 2.4	NS	4.0 ± 2.8	3.4 ± 2.5	NS
Digit span	12.9 ± 4.5	18.1 ± 4.3	0.001[b]	14.8 ± 4.8	17.0 ± 5.1	NS
Verbal fluency	23.2 ± 5.7	25.3 ± 7.1	NS	24.0 ± 5.7	26.7 ± 6.6	NS
Verbal Learn and Memory Test, first recall	6.4 ± 2.3	7.6 ± 2.1	NS	6.7 ± 1.7	7.1 ± 2.2	NS
Verbal Learn and Memory Test, long-term recall	11.3 ± 2.6	12.4 ± 2.1	NS	10.2 ± 3.3	12.3 ± 2.2	NS
AI-oW	277 ± 35	266 ± 51	NS	311 ± 83	289 ± 66	NS
AI-wW	263 ± 33	253 ± 43	NS	278 ± 46	272 ± 62	NS
Divided alertness	821 ± 101	701 ± 78	0.001[b]	816 ± 87	726 ± 93	0.03[b]
Trail Making Test	134 ± 65	92 ± 39	0.03[b]	126 ± 77	99 ± 42	NS
Self-administered depression rating scale	16.8 ± 7.7	14.3 ± 18.4	NS	10.3 ± 5.7	18.9 ± 19.2	NS
Beck Depression Inventory	10.1 ± 7.4	5.7 ± 6.7	0.02[b]	4.9 ± 3.8	6.5 ± 7.6	NS

Abbreviations: AI-oW = alertness test without a warning tone; AI-wW = alertness test with a warning tone; DM1 = myotonic dystrophy type 1; DM1 controls = group of age-, education-, and sex-matched controls for myotonic dystrophy type 1 patients; DM2 = myotonic dystrophy type 2; DM2 controls = group of age-, education-, and sex-matched controls for myotonic dystrophy type 2 patients; NS = not significant; SANFT = world test for the German word sanft.
[a]Values are mean ± SD.
[b]Significant.

the data of patients and not of controls to avoid false positive correlations.

FDG-PET scans. Dynamic PET scans were performed in 17 DM1 patients, 9 DM2 patients, and respective controls with a CTI Siemens ECAT EXACT HR+ scanner (axial spatial resolution after reconstruction 5.0 mm full width at half-maximum, field of view 15.5 cm allowing a whole-brain data acquisition, Siemens). Patients and controls were scheduled for PET after an overnight fast. Before the study, an IV cannula was placed to determine glucose plasma concentrations and for the IV application of FDG. Each subject was then positioned in the scanner in supine position. Movement artifacts were minimized using a vacuum mold adapted to the patient's head. All studies were conducted in a quiet and dimly lit environment. The subjects had their eyes closed. Prior to tracer injection, a 10-minute transmission scan with a retractable ^{68}Ge source was performed for attenuation correction. A total of 320 ± 70 MBq ^{18}FDG was injected. Image acquisition and data analysis procedures are described in appendix e-1. Correlation analysis of PET data to MRI and neuropsychological data were only performed using the data of patients and not of controls to avoid false positive correlations.

RESULTS Clinical and genetic data. All clinical data and results of neuropsychological investigations are summarized in tables 1, e-1B, and e-2. DM2 patients were significantly older (53.4 ± 10.9) than DM1 patients (37.2 ± 14.2), but the disease duration at the time of assessment was similar, reflecting the relatively later onset of DM2. Both patient groups were moderately affected concerning the skeletal muscle function as revealed by the Muscular Disability Rat-

ing Scale and DM2 patients showed a more benign course. DM1 patients had a moderate CTG repeat elongation of 574 ± 308 (ranging from 100 to 1,300).

Neuropsychological investigations. For both patient groups, we found significant deficits in global cognitive functions (world test for the German word sanft), nonverbal episodic memory (Rey-Osterrieth figure recall [ROFII], Wechsler Memory Scale [WMSII]), and alertness (divided alertness test [GA]), which were slightly more pronounced for DM1 than for DM2 patients when compared to groups of education-, age-, and sex-matched normal controls. DM1 patients showed additional deficits in MMSE, crystalline intelligence (vocabulary test [WST]), visuoconstructive ability (Rey-Osterrieth figure copy [ROFI]), verbal and nonverbal working memory (Corsi blocks, digit span), and psychomotor speed (Trail Making Test [TMT]) (table 1). For both diseases, the differences vs controls were very similar when we used the cohort of 13 normal controls for whom we had been able to perform all investigations (i.e., neuropsychology, cranial MRI, and FDG-PET scans), but who were less well matched to the patients in terms of age, gender distribution, and education (table e-1B). This result is an important prerequisite to compare neuropsychological and imaging results in the same cohorts of patients, as it confirms the homogeneity of the different control populations we used.

Correlation analysis between the neuropsychological and the clinical status revealed a significant correlation of the clinical score with frontal functions (Wisconsin Card Sorting Test for both diseases, GA only for DM1), of disease duration with alertness (alertness test with a warning tone, GA) for DM2, and of age with psychomotor speed (TMT) for both disease groups (table e-2).

MRI. ***White matter lesions.*** WML were found in 13/19 DM1 and 5/9 DM2 patients, mainly in subcortical frontal areas and centrum semiovale, less pronounced in temporal and parietal lobes. Large confluent WML were rarely present. The extent of WML was significantly correlated to psychomotor speed (TMT) in both disease groups. In DM1 patients, additional correlation of the extent of WML was found to age, disease duration, and clinical score, and in DM2 patients to visuoconstructional ability (ROFI) (table e-2).

Brain parenchymal fraction. In a previous article, we showed a significant decrease in global gray matter, as represented by the BPF, for 10 DM1 and 9 DM2 patients from the same cohorts compared to controls, which was more pronounced for DM1 patients.[27] We now confirmed these results for more patients and different and larger control groups and correlated the BPF to clinical and neuropsychological test results. We found a strong correlation to age in DM2 patients and less significant to ROFI and TMT. In DM1 patients, BPF was correlated to disease duration (table e-2). WML and BPF were correlated to each other in both disease groups.

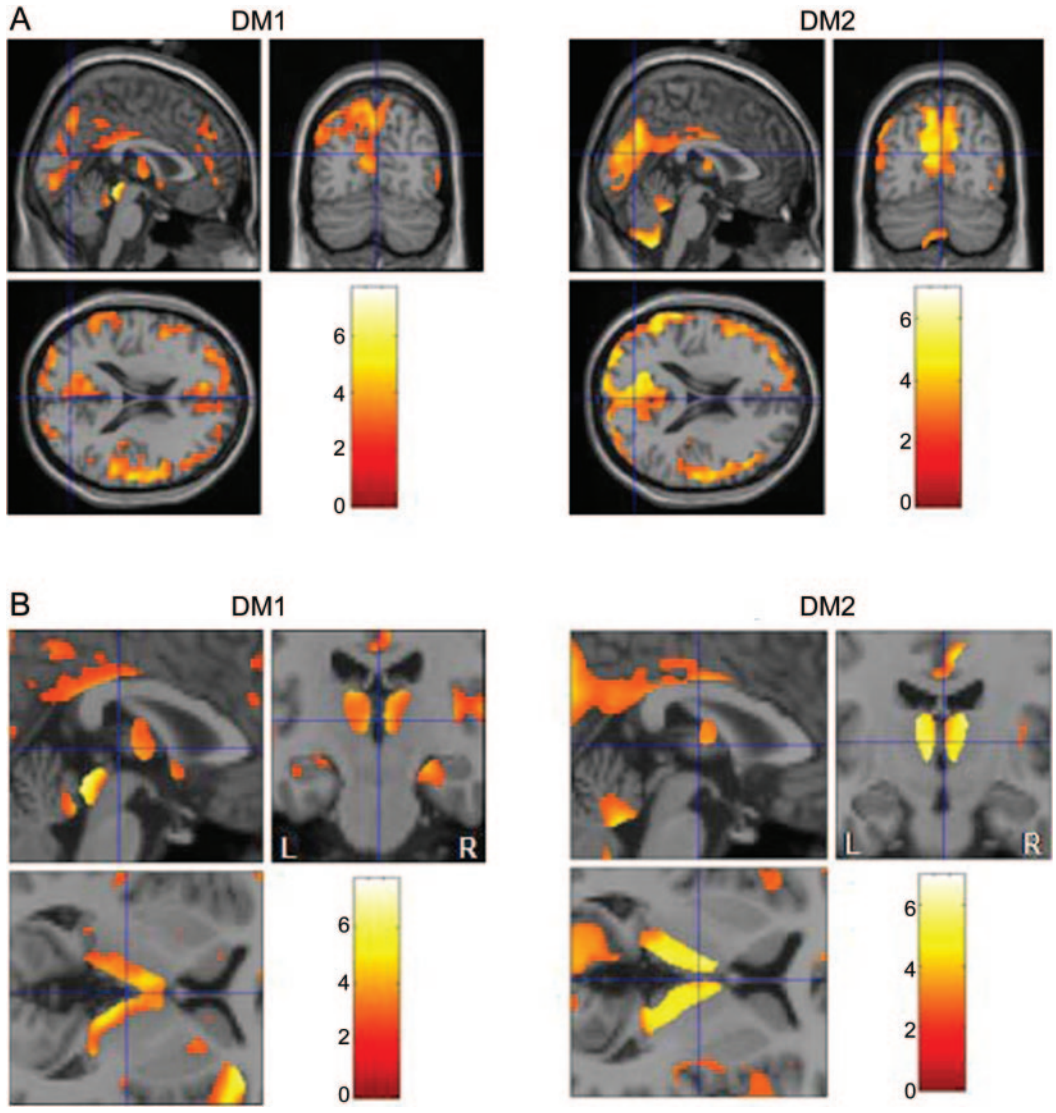
Voxel-based morphometry. In 14 DM1 and 9 DM2 patients, 3-dimensional MRI data were available for VBM analysis. Comparison of both patient groups with appropriate age-matched control groups showed a marked and widespread decrease in cortical gray matter (figure 1A, table 2). We obtained similar results when the group of 13 controls, for whom we obtained all data, was compared to both disease groups (figure e-1A), which confirms 1) our results with independent control groups and 2) the relative homogeneity of the different control groups used for MRI. In addition, VBM analysis revealed a marked symmetric alteration of gray matter in the thalami (figure 1B) in both patient groups.

A pronounced reduction of the gray matter was also found for both patient groups in the hippocampal formation bilaterally, which is shown at a higher magnification in figure 2A. Correlation analysis of the gray matter with the clinical affection status and neuropsychology using SPM revealed a significant correlation of the clinical score to atrophy in the medial and posterior parts of the right and left hippocampus in the DM1 patient group (figure 2B). Furthermore, hippocampal atrophy was correlated to deficits of nonverbal episodic memory in both patient groups, as the WMS score was correlated to left hippocampal atrophy (figure 2C) and the result of the ROFII test to bilateral hippocampal atrophy (figure 2D).

FDG-PET. SPM analysis of the cerebral glucose metabolism revealed a significant widespread and symmetric hypometabolism in the frontal lobes stretching to part of the temporal lobes for both disease groups compared to age-matched controls (figure 3A). The main finding of a bifrontal hypometabolism was reproduced in a smaller subset of patients and controls for which we could apply partial volume correction using 3-dimensional T1-weighted MRIs (figure 3B) (see Methods). Significant correlations of the hypometabolism to any of the neuropsychological test results or clinical affection status could not be identified in both disease groups.

DISCUSSION We present a comprehensive analysis of brain structure and function in myotonic dystrophy type 1 and 2 (DM1 and DM2). Our results comprise neuropsychology, structural analysis stud-

Figure 1 Voxel-based MRI analysis of the whole brain and the thalami



(A) Results from a voxel-based morphometric (VBM) analysis of 14 myotonic dystrophy type 1 (DM1) patients vs 20 age-matched healthy controls (left) and 9 myotonic dystrophy type 2 (DM2) patients vs 18 age-matched healthy controls (right) ($p < 0.05$, corrected for multiple comparisons using the False Discovery Rate, cluster threshold >100 voxels) of the whole brain (A) and the thalami (B). Areas of relative decreased gray matter were superimposed on the standard statistical parametric mapping template. *Z* scores are indexed as colors. The left side of the image is the left side of the brain.

ied by different MRI techniques, and glucose metabolism studied by PET. All investigations were performed in the same cohort of patients, allowing a comparison of the detected changes among each other and correlation analyses. Besides large cohorts of optimally matched controls for each of the different investigations, we also used one smaller core group of less well-matched controls who received all investigations. Since the differences among patients and controls were similar when using the different control groups, all obtained results can be integrated in our patient cohorts and compared with each other. A limitation of the study is the relatively small cohort of DM2 patients, implicating some caution in the interpretation of these results. However, the results fit well with the data of the larger cohort of DM1 patients and with previous studies of less extensive investigations in larger DM2 cohorts.[8,10,12-16]

The neuropsychological investigations revealed similar changes as previously described in many other reports (see Introduction and a review[10]), indicating that our cohort is representative and that the results of our imaging studies should reflect typical changes for both diseases. The conflicting results in previous studies concerning the correlation of structural or metabolic brain abnormalities, clinical features, and neuropsychology may arise mainly from the huge variability of the clinical presentation of DM based on the somatic mosaic,[6,28] but also from small cohorts of the heterogeneous patients.[18-20]

Table 2 Synopsis of regional decreases of gray matter volumes in DM1 and DM2 patients[a]

Region	Maximum	*Z* score	Cluster size
A			
Left frontal lobe	−28, 54, 4	5.20	13,047
	−11, 18, −26	3.53	257
Right frontal lobe	36, 29, −1	4.63	2,375
	45, 43, −17	3.85	4,939
	46, 22, 24	3.07	423
Left temporal lobe	−64, −37, −17	4.37	13,727
Left postcentral and precentral gyrus	−54, −8, 36	3.26	471
	−47, −7, 54	4.07	255
	−48, 9, 15	3.43	492
Right temporal lobe	61, −44, −24	3.79	2,088
Right superotemporal gyrus, right supramarginal gyrus, right postcentral and precentral gyrus	54, −3, 40	5.13	19,381
Anterior cingulum and inferior frontal gyrus	−3, 55, 12	3.39	642
	−11, 45, 16	3.38	1,431
Cingulum bilaterally	7, −19, 38	3.85	1,975
Occipital lobe and inferior parietal gyrus bilaterally	26, −93, 6	5.04	21,819
Thalamus bilaterally, hippocampus (R > L)	26, −33, −3	4.83	8,385
Cerebellum bilaterally, vermis	−1, −35, −10	5.99	2,421
B			
Left frontal lobe, left postcentral and precentral gyrus, left superotemporal gyrus, left supramarginal gyrus, thalamus bilaterally, occipital lobe bilaterally	17, −101, −6	4.86	131,039
	−15, 51, −23	3.11	384
Right frontal lobe, right superotemporal gyrus, right supramarginal gyrus, right postcentral and precentral gyrus	62, −27, 41	4.97	30,618
	7, 58, 30	3.05	1,165
	22, 46, 34	2.66	327
Left temporal lobe	−59, −2, −11	3.00	311
	−38, 16, −25	2.63	340
Right temporal lobe	45, −69, −8	2.92	1,330
	55, −51, −18	2.72	413
	43, −27, −31	3.38	452
Cerebellum bilaterally, vermis	−10, −50, −59	5.15	11,807
Left parietal lobe	−23, −53, 62	4.16	506
Left caudatum	−12, 3, 18	3.71	287
Right parietal lobe, right postcentral gyrus	15, −57, 60	3.52	1,104
Right cingulum	−6, −16, 39	3.52	488

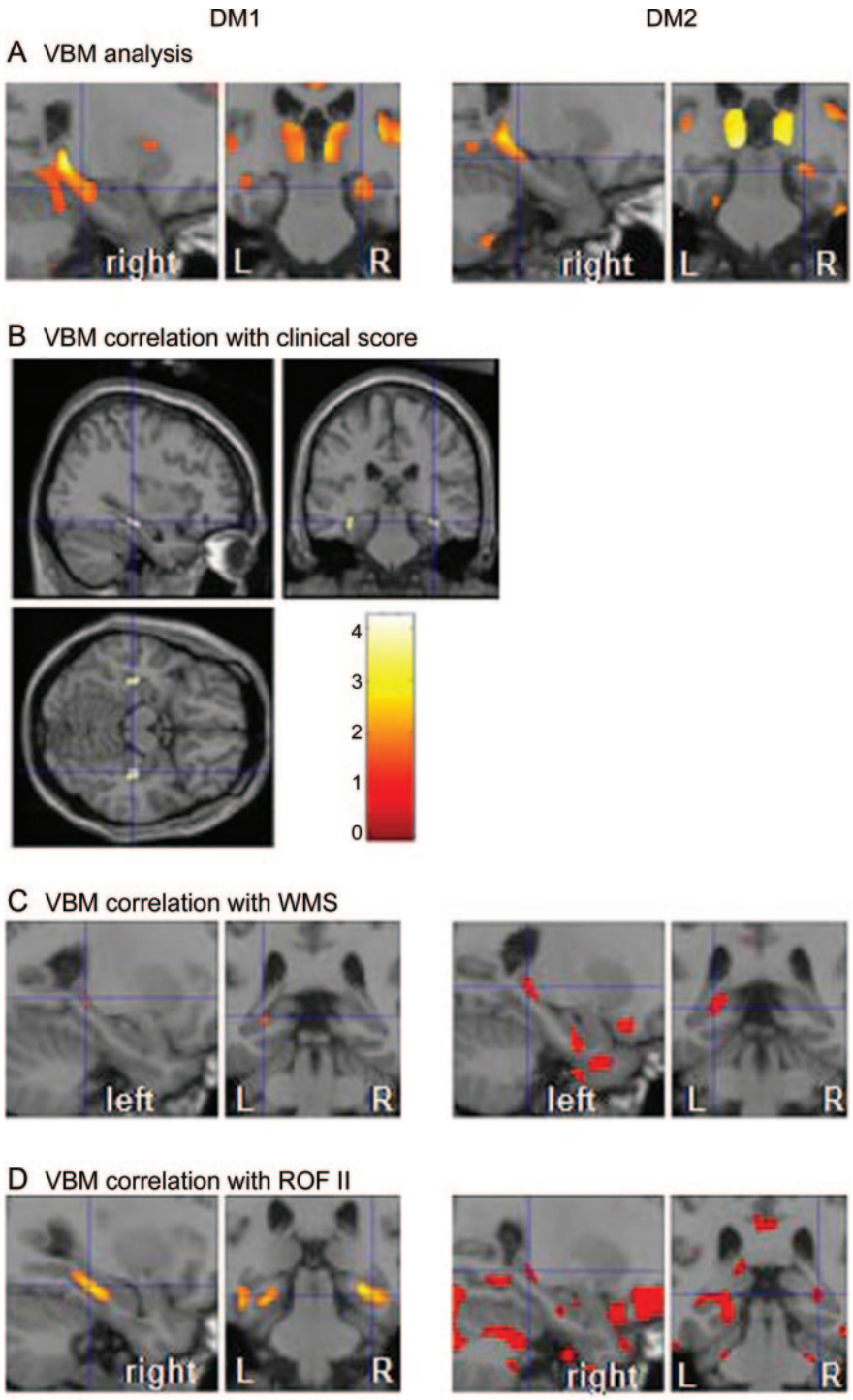
Abbreviations: DM1 = myotonic dystrophy type 1; DM2 = myotonic dystrophy type 2.
[a]The table lists the results from voxel-based morphometric analysis of (A) 14 DM1 patients vs 20 age-matched healthy controls and (B) 9 DM2 patients vs 18 age-matched healthy controls sorted by anatomic areas. This corresponds to a textual representation of the results shown in figure 1. More than 1 anatomic area is listed in a row if a cluster of significant voxels stretches to several anatomic areas. Several clusters are listed in a row if an anatomic area contains several clusters (or relevant parts of clusters); e.g., the first row of (A) indicates that the voxel-based morphometry analysis of DM1 patients showed 2 independent clusters of voxels with significantly reduced gray matter in the left frontal lobe (most likely corresponding to atrophy in these regions). The last but one row of (A) shows that the analysis yielded a cluster of voxels with significantly reduced gray matter that included (relevant parts of) the thalami and both hippocampi. The table lists the maximum of each cluster, given as coordinates of the standardized stereotaxic atlas, the significance level as expressed by *Z* scores for each cluster greater than 250 voxels ($p < 0.05$, corrected for multiple comparisons using the False Discovery Rate, cluster threshold >250 voxels), and the size of the clusters given as the number of voxels.

Our imaging studies revealed widespread cerebral abnormalities, but most important, they also identified specific changes that might explain some of the characteristic neuropsychological dysfunctions in these patients. In this regard, the extent of WML was correlated to psychomotor speed, fitting well with the hypothesis that subcortical abnormalities are an important determinant of such dysfunction, as has been also found in subcortical vascular disease.[29] Structural analysis based on VBM has been published for DM1 and DM2 patients, demonstrating widespread gray matter changes.[30-32] However, cognitive dysfunctions were not analyzed in parallel in these studies. In our cohort, VBM analysis revealed generalized decreases of gray matter including the hippocampal formation and the thalami in both patient groups compared to matched control groups. We developed a clinical score for disease severity based on the number of CTG repeats, disease duration, and age. Interestingly, the correlation analysis of changes detected in VBM in DM1 patients to this clinical score revealed highly symmetric areas in both hippocampal formations, thus highlighting hippocampal pathology as an important disease parameter in DM1. In addition, the deficits in nonverbal episodic memory were correlated to the hippocampal decrease in gray matter in both patient groups. Since the hippocampus plays a crucial role in episodic memory, this finding may provide a plausible explanation for these characteristic and most prominent neuropsychological deficits in both DM1 and DM2 patients.

VBM analysis also revealed a marked gray matter alteration in the thalami in both patient groups. Cell loss has been reported in the thalami in DM1 patients[33] and ribonuclear foci of mutant DMPK transcripts are found in the thalami.[34] It is therefore conceivable that the findings of our VBM analysis might rather reflect tissue alterations than atrophy.

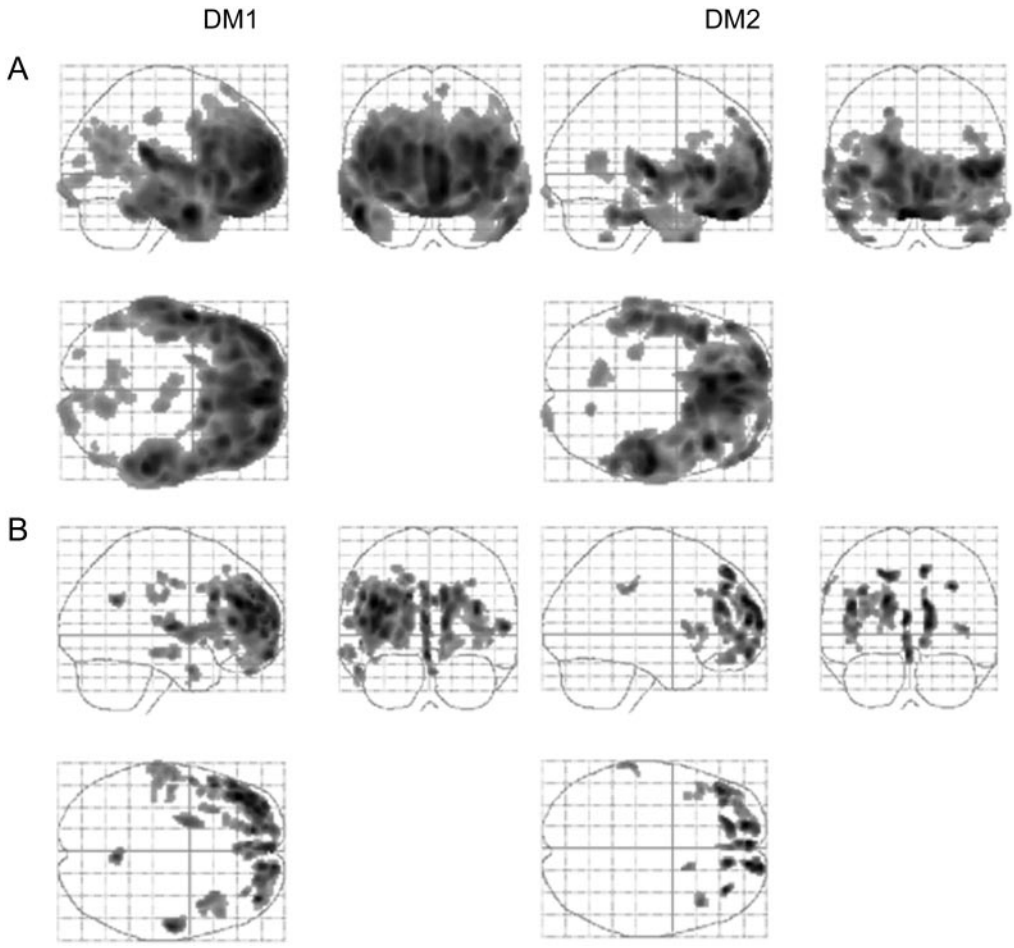
Earlier studies in DM1 patients using FDG-PET with a region of interest analysis[12-14] suggested a predominantly temporofrontal hypometabolism. For DM2 patients, so far only a case report described comparable results.[24] In the present study, we evaluated the whole brain employing SPM, which revealed large areas of hypometabolism in the frontal extending to the temporal lobes in FDG-PET images of DM1 and DM2 patients compared to matched control groups. Since the VBM analysis suggested a critical decrease in gray matter (most likely representing cortical atrophy), the question arises if the hypometabolism is simply a matter of this atrophy or an independent phenomenon. Therefore, it is important to note that our findings were reproduced in a smaller subset of the patients for which we could apply partial volume correction using 3-dimensional T1-weighted images. Furthermore, the gray matter

Figure 2 Voxel-based MRI analysis of the hippocampi



Results from voxel-based morphometric (VBM) analyses of myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) patients highlighting the abnormalities detected in the gray matter of the hippocampal formations. *Z* scores are indexed as colors. The left side of the image is the left side of the brain. (A) Enlarged view of a comparison of the gray matter of 14 DM1 patients with 20 age-matched controls and 9 DM2 patients with 18 age-matched controls ($p < 0.01$, uncorrected for multiple comparisons) indicating bilateral (right > left) hippocampal atrophy in both patient groups. (B) Results of a correlation analysis of the clinical score with gray matter determined by VBM in 14 DM1 patients. The images indicate that the clinical score correlates with bilateral symmetric hippocampal atrophy ($p < 0.05$, uncorrected for multiple comparisons). (C) Results of a correlation analysis of the Wechsler Memory Scale (WMS) score (nonverbal episodic memory test) with gray matter determined by VBM in 12 DM1 patients (left) and 9 DM2 patients (right). The WMS score correlates with left hippocampal atrophy in both patient groups ($p < 0.05$, uncorrected for multiple comparisons). (D) Results of a correlation analysis of the Rey-Osterrieth figure recall (ROF II) score (nonverbal episodic memory test) with gray matter determined by VBM in 14 DM1 patients (left) and 9 DM2 patients (right). The ROF II score correlates with bilateral hippocampal atrophy in both patient groups ($p < 0.05$, uncorrected for multiple comparisons).

Figure 3 ^{18}F-deoxy-glucose positron emission tomography (FDG-PET) analysis



Comparisons of FDG-PET images between different cohorts of myotonic dystrophy type 1 (DM1) (left) and myotonic dystrophy type 2 (DM2) (right) patients to normal controls without (A) and with (B) partial volume correction. A statistical parametric mapping (SPM) group analysis with $p < 0.05$, corrected for multiple comparisons using the False Discovery Rate, and a cluster threshold >30 voxels were used. The images show areas of relative hypometabolism of patients vs controls as SPM glass brains in maximum intensity projection. (A) 17 DM1 patients vs 18 age-matched controls (left) and 9 DM2 patients vs 16 age-matched controls (right) without correction for partial volume effect. (B) 12 DM1 patients vs 13 controls (left) and 9 DM2 patients vs 13 controls (right) after correction for partial volume effects. For these groups of patients and controls, MRIs were available and were used in 2 steps, 1) to match individual PET images with MRIs and 2) to perform partial volume correction. As expected, the areas of hypometabolism are much smaller when the decrease in gray matter observed on MRI is considered. In figure e-1B, we show in addition the results without partial volume correction using the same groups of patients vs controls.

decrease as indicated by VBM clearly has a different pattern than the hypometabolism found in the PET study. These results thus indicate that the hypometabolism is an independent phenomenon of the disease and not solely a result of atrophy.

Our study revealed similar neuropsychological deficits, structural brain abnormalities, and hypometabolism in both diseases, which were however more pronounced in DM1 than in DM2 patients. The neuropsychological and brain imaging studies performed in the same cohort of patients support the hypothesis of a widespread disease process with predominance in frontal and temporal lobes including gray and white matter, which provides the basis for the cognitive deficits in DM1 and DM2. Specifically, our investigations suggest a characteristic decline in nonverbal episodic memory as a result of bilateral hippocampal atrophy in both diseases that is also correlated to the clinical disease severity. WML could be the main reason for the slowing of psychomotor speed. Up to now, the pathophysiology of the cerebral degeneration in DM1 and DM2 is not known. Widespread distribution of mutant RNA[34] and tau variant accumulations have been described[35] which could represent a molecular correlate of the observed cerebral abnormalities.

ACKNOWLEDGMENT

The authors thank Drs. G. Grön, M. Riepe, D. Bittner, and I. Uttner for advice with selection of the neuropsychological test battery, Drs. E. Kraft

and N. Mitrovic for help with evaluation of the white matter lesions, and Dr. J. Gostomzyk for referring controls.

DISCLOSURE

Dr. Weber and Dr. Roebling report no disclosures. Dr. Kassubek serves on scientific advisory boards for GlaxoSmithKline and Boehringer Ingelheim and has received speaker honoraria from GlaxoSmithKline, Boehringer Ingelheim, and UCB. Dr. Hoffmann, Dr. Rosenbohm, Dr. Wolf, Dr. Steinbach, and Dr. Jurkat-Rott report no disclosures. Dr. Walter has received travel expenses and/or honoraria for lectures or educational activities not funded by industry; serves as an Associate Editor of *Nervenheilkunde* and on the editorial board of *Current Psychiatry Reviews*; receives royalties from the publication of *Neurophilosophie der Willensfreiheit* (Mentis, 1998) and *Funktionelle Bildgebung in Psychiatrie und Psychotherapie* (Schattauer, 2005); and receives research support from the German Ministry of Education and Research (BMBF), the Commission of the European Communities, the German Research Foundation (DFG), and the Volkswagen Foundation. Dr. Reske serves on the editorial boards of the *European Journal of Nuclear Medicine and Molecular Imaging* and *Nuklearmedizin* and has received research support from Boehringer Ingelheim (technical equipment), the Bundesministerium für Wirtschaft und Technologie (BMWi), the German Research Foundation (DFG), the Arbeitsgemeinschaft industrieller Forschungsvereinigungen (PRO INNO II), the European Community's FP6 funding, Deutsche Jose Carreras Leukämie-Stiftung e.V., and Deutsche Krebshilfe. Dr. Lehmann-Horn serves on the editorial board of *Neurology*®. Dr. Mottaghy reports no disclosures. Dr. Lerche serves on scientific advisory boards for Pfizer Inc., Janssen, UCB, Novartis, Valeant Pharmaceuticals International, GlaxoSmithKline, and Eisai Inc.; has received funding for travel GlaxoSmith Kline and UCB; has received honoraria for speaking engagement or educational activities from Pfizer Inc., Desitin Pharmaceuticals, GmbH, UCB, and GlaxoSmithKline; and has received research support from Sanofi-Aventis and UCB.

Received July 30, 2009. Accepted in final form December 7, 2009.

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CDC, AAN to Health Care Professionals: Monitor Patients for GBS

The Centers for Disease Control and Prevention (CDC) and the American Academy of Neurology (AAN) collaborated to reach out to neurologists across the US to monitor and report any possible new cases of Guillain-Barré syndrome (GBS) following 2009 H1N1 flu vaccination.

Neurologists and health care professionals nationwide who diagnose patients with vaccine-associated GBS should use the CDC and FDA Vaccine Adverse Event Reporting System (VAERS) to report their observations.

In addition, neurologists and all health practitioners in the 10 Emerging Infections Program (EIP) states—California, Connecticut, Maryland, Minnesota, New Mexico, New York, Colorado, Oregon, Georgia, and Tennessee—are asked to report all new cases of GBS, regardless of vaccination status, to their state's surveillance officer.

The AAN hosted a series of webinars providing an in-depth look at H1N1 vaccination and how it may pose a risk for GBS and information about the vaccination monitoring campaign.

For additional information about the monitoring campaign, or to watch the webinars or download VAERS form and information on reporting to surveillance officers in your state, visit the AAN's GBS toolkit page, *www.aan.com/view/gbstoolkit*.

Comparative analysis of brain structure, metabolism, and cognition in myotonic dystrophy 1 and 2

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Neurology 2010;74;1108-1117; originally published online Mar 10, 2010;
DOI: 10.1212/WNL.0b013e3181d8c35f