Brain Advance Access published June 7, 2006

doi:10.1093/brain/awl148 *Brain* (2006) Page 1 of 12

Morphological basis for the spectrum of clinical deficits in spinocerebellar ataxia 17 (SCA17)

K. Lasek,[1] R. Lencer,[2] C. Gaser,[4] J. Hagenah,[1] U. Walter,[5] A. Wolters,[5] N. Kock,[1,3] S. Steinlechner,[2] M. Nagel,[2] C. Zühlke,[3] M.-F. Nitschke,[1] K. Brockmann,[5] C. Klein,[1,3] A. Rolfs[5] and F. Binkofski[1]

Departments of [1]Neurology and NeuroImage Nord, [2]Psychiatry and Psychotherapy, [3]Institute of Human Genetics, University Hospital of Schleswig-Holstein, Campus Luebeck, Luebeck, [4]Department of Psychiatry, Friedrich-Schiller University of Jena, Jena and [5]Department of Neurology, University of Rostock, Rostock, Germany

Correspondence to: Ferdinand Binkofski, MD, Department of Neurology and NeuroImage Nord, University Hospital of Schleswig-Holstein, Campus Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany
E-mail: ferdinand.binkofski@neuro.uni-luebeck.de

Spinocerebellar ataxia 17 (SCA17) is a rare genetic disorder characterized by cerebellar, extrapyramidal, pyramidal as well as psychiatric signs. The pathoanatomical basis of this disorder is still not well known. A total of 12 patients and 12 age- and sex-matched controls were examined by *in vivo* MRI voxel-based morphometry (VBM). Besides general patterns of disease-related brain atrophy, characteristic syndrome-related morphological changes in SCA17 patients were studied. In comparison with normal controls, SCA17 patients showed a pattern of degeneration of the grey matter centred around mesial cerebellar structures, occipito-parietal structures, the anterior putamen bilaterally, the thalamus and other parts of the motor network, reflecting the cerebellar, pyramidal and extrapyramidal signs. A correlation analysis revealed a clear association between the clinical cerebellar, extrapyramidal and psychiatric scores and degeneration in specific areas. Two degeneration patterns were found as follows: regarding motor dysfunction, atrophy of the grey matter involved mainly the cerebellum and other motor networks, in particular the basal ganglia. In contrast, correlations with psychiatric scores revealed grey matter degeneration patterns in the frontal and temporal lobe, the cuneus and cingulum. Most interestingly, there was a highly significant correlation between the clinical Mini-Mental State Examination scores and atrophy of the nucleus accumbens, probably accounting for the leading psychiatric signs.

Keywords: basal ganglia; cerebellar atrophy; nucleus accumbens; SCA17; voxel-based morphometry

Abbreviations: FDR = false discovery rate; GAF = Global Assessment of Functioning; GAS = Global Assessment Scale; ICARS = International Cooperative Ataxia Rating Scale; MMSE = Mini-Mental State Examination; SCA = spinocerebellar ataxia; SVC = small volume correction; UPDRS III = Unified Parkinson's Disease Rating Scale; VBM = voxel-based morphometry

Received November 29, 2005. Revised April 26, 2006. Accepted May 8, 2006

Introduction

Autosomal dominant spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative disorders characterized by progressive ataxia and various other phenotypical features generally with adult age of onset. More than 25 SCA types have been described (Manto, 2005; Yu *et al.*, 2005). Current molecular classification corresponds to the order of gene description (Manto, 2005).

SCA17 is caused by an expanded polyglutamine in the TATA-binding protein (TBP), a general transcription initiation factor (Koide *et al.*, 1999; Nakamura *et al.*, 2001). In addition to cerebellar ataxia, the variable phenotypic spectrum of this rare disorder also includes extrapyramidal movement disorders (Nakamura *et al.*, 2001; Zuhlke *et al.*, 2001; Hernandez *et al.*, 2003), such as dystonia (Hernandez *et al.*, 2003; Hagenah *et al.*, 2004), chorea (Toyoshima *et al.*, 2004) and spasticity, but also epilepsy (Maltecca *et al.*, 2003; Rolfs *et al.*, 2003; De Michele *et al.*, 2003), and psychiatric disorders (Maltecca *et al.*, 2003; Rolfs *et al.*, 2003). Accordingly, a remarkable phenotypic overlap exists with other neurodegenerative disorders such as Huntington's disease (Stevanin *et al.*, 2003; De Michele et al., 2003) and Parkinson's disease (Hernandez *et al.*, 2003).

Post mortem examinations of SCA17 patients demonstrated cerebellar, cortical and subcortical atrophy, cerebellar and cerebral cell loss and also gliosis (Bruni *et al.*, 2004).

MRI allows one to study brain morphology in neurodegenerative disorders *in vivo*. In SCAs, the most consistent feature is cerebellar atrophy. In addition, extracerebellar structures are frequently involved to a variable degree, according to the type of SCA. Previous MRI studies revealed significant differences in the pattern and extent of the morphological alterations associated with different SCA mutations (SCA1–SCA3, SCA6, SCA7). MRI-based volumetric studies revealed more severe atrophy of the cerebellum and brainstem in SCA2 than in SCA1 and SCA3 (Klockgether *et al.*, 1998; Murata *et al.*, 1998), and there is relatively selective involvement of the cerebellum in SCA6 (Murata *et al.*, 1998). Moreover, putaminal and caudate volume was reduced only in SCA3, but not in SCA1 and SCA2 (Klockgether *et al.*, 1998). In patients with SCA7, the pontine volume was decreased to a greater extent than in patients with other types of SCA (Bang *et al.*, 2004).

To date, a systematic study of morphometric changes is lacking in SCA17 patients. In this study, we investigated 12 SCA17 patients from northern Germany in order to identify the specific pathoanatomical features of this disease by using voxel-based morphometry (VBM). Although the leading syndrome of this rare genetic disorder is cerebellar ataxia, there are also a variety of additional motor and psychiatric signs that underline the systemic character of this disease. Therefore, we expected to find not only signs of cerebellar degeneration but also pathological changes in other regions of the brain, which could explain the spectrum of neurological and psychiatric signs. First, we performed a categorical comparison of the grey matter images between SCA17 patients and age- and sex-matched control subjects in order to identify the general pattern of atrophy characteristic for this disease. Secondly, we aimed at elucidating cerebral structures significantly involved in motor and psychiatric syndromes by correlating morphometric data with specific clinical scales.

Methods

Subjects and patients

The SCA17 patients were recruited from the out-patient movement disorders clinics at the Departments of Neurology, University Hospital of Rostock and Luebeck, Germany, where the patients have been diagnosed and are followed up on a regular basis. Five patients were members of one family and three patients belonged to another one. Another four patients came from unrelated families.

Twelve individuals with SCA17 [six male, six female, mean age: 41.1 years (± 14.6)] and twelve age- and sex-matched healthy volunteers [six male, six female, mean age: 41.9 years (± 12.6)] were studied. Age differences between the two groups were not significant ($P = 0.88$).

Total genomic DNA was extracted from peripheral blood leucocytes by standard protocols. Molecular genetic SCA17 testing was performed as published previously (Koide *et al.*, 1999). All 12 patients were known carriers of a pathological repeat expansion in the *SCA17* gene (Rolfs *et al.*, 2003). All controls tested negative for *SCA17* mutations.

All patients were personally interviewed and clinically examined by C.K., J.H., N.K. and A.H. to evaluate the neurological status using a standardized examination procedure. Ataxia was assessed quantitatively by applying the International Cooperative Ataxia Rating Scale (ICARS) of the World Federation of Neurology. According to the Ashworth score, spasticity was diagnosed based on hyperactive muscle stretch reflexes, increased resistance to passive movement and, occasionally, simultaneous activation of opposing antagonistic muscle groups. Further, the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS III) was used to quantify extrapyramidal signs (e.g. tremor, rigidity, bradykinesia).

Each subject underwent a comprehensive psychiatric assessment by an experienced psychiatrist (R.L., M.N. or S.S.) using the German version of the Structured Clinical Interview for DSM-IV Axis I and II Disorders (American Psychiatric Association, 1994). Furthermore, all subjects were administered a standardized clinical psychiatric examination including neuropsychological screening for dementia (Mini-Mental State Examination; MMSE) (Folstein *et al.*, 1975). Raw data were converted into per cent ranges since some items were not applicable to all subjects due to motor impairment. For the three patients (no. 4, 5 and 9) who were unable to complete all sections of the MMSE due to severe motor dysfunction, the probable reachable score was estimated (Table 1). A cut-off of 80% corresponding to a rate of 24 out of 30 points was used to define a diagnosis of dementia. A diagnosis of 'personality change' was made when a persistent personality disturbance was clinically evident or reported by the caregivers and the changes were severe enough to cause clinically important distress or impairment in social, occupational or other important areas of functioning. Furthermore, we defined a 5-point score according to five out of the six F07 criteria for a personality change due to brain disease or disorder provided by the International Classification of Diseases, 10th edition (ICD-10) (World Health Organization, 1992). The sixth item which refers to altered sexual behaviour was excluded because we did not receive sufficient information from all subjects. The diagnosis of a personality change was made independently of the diagnosis of dementia or cognitive impairment. In addition, the Global Assessment of Functioning (GAF) referring to the four weeks prior to examination was determined (American Psychiatric Association, 1994). The GAF is a revised version of the Global Assessment Scale (GAS) that was used as the Axis V of DSM-III to assess a patient's overall functioning. The GAF is a 5-point scale where a '5' represents full global functioning, a '3' average global functioning and a '1' complete lack of global functioning. High scores represent individuals who are generally without psychopathology, whereas low scores indicate an immediate danger of suicide, harming others or inability to maintain basic human needs. Further, collateral information from caregivers was collected to confirm the clinical diagnosis. Caregivers were specifically asked about distinct and enduring changes in behaviour and personality over recent years. A consensus diagnosis was established by R.L. and M.N. or R.L. and S.S. who were blind to the neurological diagnosis.

The study was approved by the local ethics committee and written informed consent was obtained from all participating subjects in accordance with the Declaration of Helsinki.

Table 1 Demographics and clinical findings of 12 patients with SCA17

No.	Sex	Age (years)	Leading motor/ special symptoms	Leading psychiatric symptoms	Clinical scales						
					Disease duration (years)	Ataxia	Spasticity	UPDRSIII	MMSE (%)	GAF (%)	F07
1	W	50	Cerebellar syndrome	Dementia, personality change	18	71	2	43	13.33	30	4
2	W	54	Cerebellar syndrome, bradykinesia	Dementia	7	54	1	39	60.71	40	2
3	M	42	Spasticity, bradykinesia	Agoraphobia, adjustment disorder	7	9	1	9	100.0	90	2
4	M	50	Spasticity, epilepsy	Dementia, personality change	20	44	3	59	26.67	20	4
5	M	47	Cerebellar syndrome	Dementia, personality change	19	50	2	44	33.33	30	5
6	W	45	Cerebellar syndrome	Dementia, personality change	20	59	1	48	75.0	50	4
7	M	23	Mild cerebellar syndrome	Specific phobia, dysthymia	4	3	0	4	100.0	90	0
8	M	20	None	Adjustment disorder	2	0	0	0	100.0	100	0
9	W	22	Cerebellar syndrome, parkinsonism	Social phobia, adjustment disorder	1	36	0	19	100.0	70	2
10	M	45	Mild dysarthria, mild spasticity	Obsessive personality disorder	5	4	1	1	100.0	90	0
11	W	66	Cerebellar syndrome	Dementia, personality change	21	41	1	38	60.71	50	3
12	M	28	Cerebellar syndrome, segmental dystonia	Cognitive decline	7	51	1	47	89.29	70	1

Ataxia = ICARS of the World Federation of Neurology; spasticity score: 0 = none, 1 = mild, 2 = moderate, 3 = severe; F07 = number of criteria fulfilled for an organic personality change.

MRI scanning

Scanning was performed with a 1.5 T whole-body scanner (Symphony, Siemens; Erlangen, Germany). All subjects underwent structural MRI using a T_1-weighted FLASH 3D MR sequence [echo time (TE) = 5 ms; repetition time (TR) = 15 ms; flip angle = 30°; isotropic voxel size $1 \times 1 \times 1$ mm^3].

Images were then analysed using VBM, a fully automated technique for computational analysis of differences in local grey matter volume.

The spatial normalization to the standard anatomical space was performed in a two-stage process. First, each image was normalized using the International Consortium for Brain Mapping template (Montreal Neurological Institute, Montreal, Canada), which approximates Talairach space. We applied a 12-parameter affine transformation to correct image size and position. Regional volumes were preserved, while corrections for global differences in whole brain volume were made. The normalized images of all subjects and patients were averaged and smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM) and then used as a new template with reduced scanner- and population-specific bias. Secondly, each image was locally deformed to the new template using a non-linear spatial transformation (Ashburner and Friston, 1999). This accounted for the remaining shape differences between the images and the template, and improved the overlap of corresponding anatomical structures (Hellier *et al.*, 2003). Finally, using a modified mixture model cluster analysis, normalized images were corrected for non-uniformities in signal intensity and partitioned into grey and white matter, CSF and background. To remove unconnected non-brain voxels (e.g. rims between brain surface and meninges, which are connected only by few voxels to the clusters of grey and white matter), we applied a series of morphological erosions and dilations to the segmented images (Good *et al.*, 2001*a*, *b*). For investigations of more focal changes of the grey matter images were smoothed with a Gaussian kernel of 8 mm FWHM and for the assessment of more global changes with a Gaussian kernel of 12 mm FWHM.

Using a general linear model, a voxel-by-voxel one-way ANOVA was computed to detect differences in grey matter volume between groups. An absolute grey matter threshold of 0.25 was used to avoid possible edge-effects around the border between grey and white matter or CSF. Additionally, a correlation between morphometric data and the clinical scores (ataxia, spasticity, UPDRS III, MMSE, GAF, F07) was performed using a simple regression algorithm (SPM2) and the corresponding correlation coefficient was calculated with the software package SPSS (Version 12.0).

Small volume correction (SVC) was also employed, when having a strict *a priori* hypothesis, to an anatomically restricted area of expected changes in grey matter volume. We performed SVC in volumes of 10 mm diameter. To correct for multiple comparisons we applied the false discovery rate (FDR) approach, which controls for the expected proportion of false positives among suprathreshold voxels (Benjamini and Hochberg, 2000).

The WFU PickAtlas (Maldjian *et al.*, 2003) and the Schmahmann *et al.* (2000) MRI atlas of the human cerebellum (Schmahmann *et al.*, 2000) were used as an anatomical reference to assess the exact localization of significantly atrophic grey matter areas.

Results

Patients

Nine individuals with *SCA17* mutations were clinically definitely affected, two were mildly affected, and one mutation carrier was classified as unaffected. The leading clinical signs as well as demographics and clinical variables are summarized in Table 1. Most of our SCA17 patients clearly showed cerebellar, extrapyramidal and pyramidal signs. Ataxia was observed in 11 out of the 12 SCA17 patients, 9 patients showed spasticity and 11 extrapyramidal signs. Dementia (MMSE < 80%) was observed in 6 out of the 12 patients (50%). A personality change according to the definition provided by the F07-item of the ICD-10 (three or more criteria fulfilled) was observed in five of the patients. Additionally, three patients met two of the criteria and another one a single criterion. Other psychiatric diagnoses were as follows: agoraphobia (1), specific phobia (1), social phobia (1), dysthymia (1), adjustment disorder (3) and obsessive–compulsive personality disorder (1). Global psychiatric functioning (GAF-score) was <85% in eight of the patients. In total, a psychiatric lifetime disorder was observed in 11 out of the 12 SCA17 patients. In one patient without manifested psychiatric diagnosis, an intellectual decline (89% in MMSE) was found suggesting a possible development of dementia.

Morphometric data

Categorical comparison

The categorical comparison between the SCA17 patients and the normal subjects revealed a pattern of degeneration that was centred around the mesial and posterior cerebellar structures, including the vermis, and most prominently accentuated on the left side (Fig. 1). Maximum atrophy was found in the left cerebellar posterior lobe, lobule VIII ($x, y, z = -15, -66, -45$, $Z = 6.48$, $P_{FDR} = 0.01$), similar to the findings on the right side, lobule VIII ($x, y, z = 13, -47, -5$–53, $Z = 4.15$, $P_{FDR} = 0.01$, SVC). Moreover, large regions with reduced grey matter volume were observed in the occipito-parietal structures bilaterally. Furthermore, a clear reduction of the grey matter volume was found in the thalamus on the left side ($x, y, z = -19, -32, 10$, $Z = 3.25$, $P_{FDR} = 0.01$) and in the anterior putamen bilaterally, more

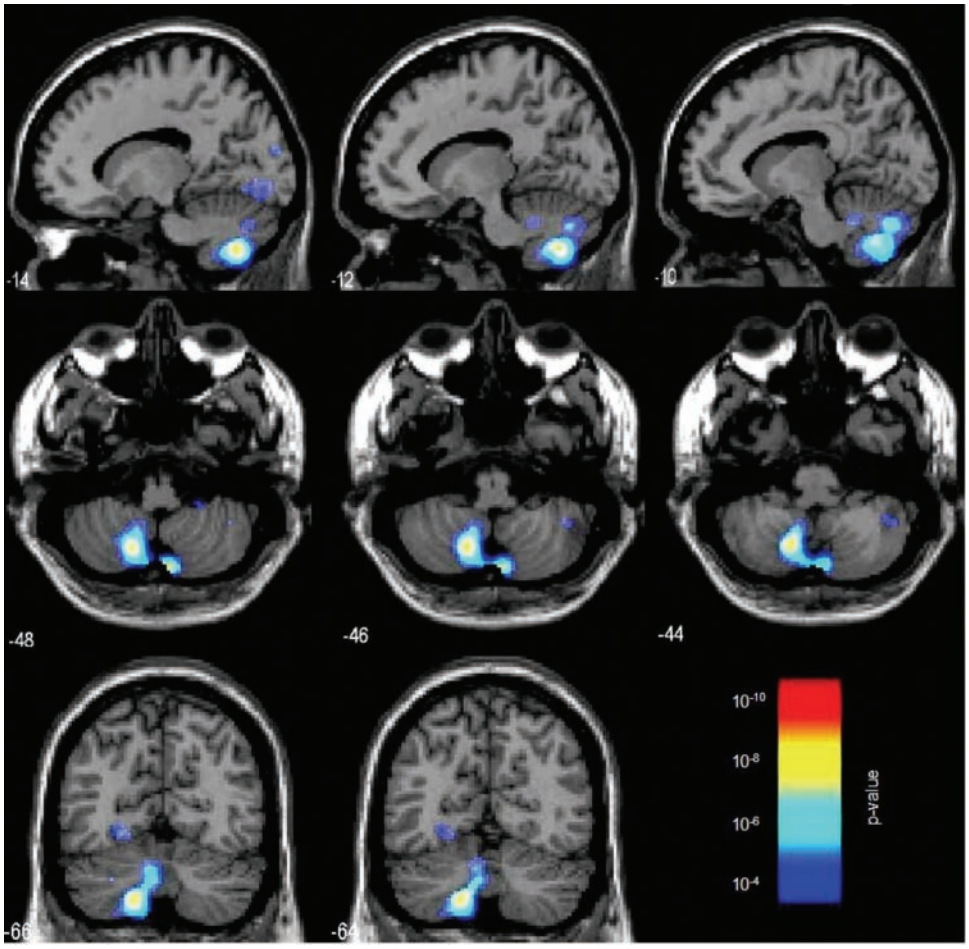

Fig. 1 Visual presentation of the VBM categorical comparison between the SCA17 patients and the controls in orthogonal sections (sagittal, coronal and axial view). To emphasize the most significant results, we used a high threshold of $P_{FDR} = 0.01$. The colour bar represents the *P* values.

pronounced on the left side (left: *x, y, z* = −20, 17, −7, *Z* = 4.01, P_{FDR} = 0.01, SVC; right: *x, y, z* = 20, 14, 5, *Z* = 3.88, P_{FDR} = 0.01, SVC). An overview of the morphometric analysis of the SCA17 patients and the controls by anatomical region is listed in Table 2.

Clinical correlations

Clinical correlations for the most leading phenotypic features including ataxia, extrapyramidal and psychiatric signs were calculated using simple regression analysis. Details of the morphometric analysis are given in Table 2. Figure 2 displays a visual presentation of the voxel-by-voxel correlation between the grey matter values and the individual MMSE values.

Ataxia

We rated the severity of cerebellar ataxia of SCA17 patients based on the ICARS (Trouillas *et al.*, 1997). The patients showed a wide phenotypic spectrum ranging from mild to severe cerebellar signs with total scores lying between 4 and 71 on the ICARS with a mean of 35.17 (SD = 24.71). One patient did not show any cerebellar signs (Table 1). The total scores of the ICARS subscales were summarized and correlated with the morphometric data and revealed significant cerebellar atrophy. The highest degree of atrophy, correlating with the ataxia ICARS score, was detected in the posterior lobe of the right cerebellum, lobule VIII (*x, y, z* = 11, −74, −49, *Z* = 4.02, P_{FDR} = 0.005, SVC), whereas the left side (lobule VIII) was also impaired, but to a lesser extent (*x, y, z* = −12, −65, −50, *Z* = 3.42, P_{FDR} = 0.005, SVC) (Table 2). The coefficient of correlation was negative (*R* = −0.75), describing the strength of linear relationship between the clinical score and the morphometric data (Fig. 4).

Spasticity

In order to rate signs of spasticity in accordance with the Ashworth score (Bohannon and Smith, 1986), SCA17 patients were divided into four groups as follows: unaffected, mild, moderate and severe signs. The score ranged from no spasticity to severe. Most of our patients showed mild spasticity signs, the calculated mean was 1.08 (SD = 0.90) (Table 1). A simple regression analysis revealed strong relationships between the spasticity and the morphometric data located in the putamen on both sides (right hemisphere: *x, y, z* = 17, 7, −13, *Z* = 4.80, P_{FDR} = 0.005, SVC and left hemisphere: *x, y, z* = −21, 12, −2, *Z* = 4.24, P_{FDR} = 0.005, SVC) (Table 2). The coefficient of correlation revealed a negative correlation (*R* = −0.89) (Fig. 4).

UPDRS III

Individual UPDRS motor scores (mean = 29.25, SD = 21.18; Table 1) (Fahn and Elton, 1987) were correlated with morphometric data to detect any degeneration pattern in the extrapyramidal system. A significant negative correlation was observed in the left putamen (*x, y, z* = −21, 6, 4, Z = 4.48, P_{FDR} = 0.005, SVC; *R* = −0.71) (Table 2, Fig. 4).

MMSE

The mean MMSE per cent was 71.6% (SD = 32.3) with scores ranging from 100 to 13.3%. A simple regression analysis for correlations of grey matter volume with the MMSE clinical score revealed a highly significant relationship within the left ventral striatum (Table 2). The maximum atrophy was located in the nucleus accumbens (*x, y, z* = 11, 6, −12, *Z* = 5.47, P_{FDR} = 0.01) with a highly positive coefficient of correlation (*R* = 0.98) (Figs 2 and 4).

Personality change (F07)

All of the nine patients who met at least one criterion of a personality change had a consistently reduced ability to persevere with goal-directed activities. Seven patients showed emotional changes, mostly emotional lability, irritability or apathy. The behaviour of two patients was characterized by a disinhibited expression of needs or impulses without considering consequences or social conventions. In six patients, cognitive disturbances were observed in the form of excessive suspiciousness or preoccupation with a single theme. Another three patients showed a marked alteration of the rate and flow of language production, independent of the dysarthria due to the SCA (Table 1). Correlation with the morphometric data identified significant relationships which were most pronounced on the right side in the paracentral lobule of the frontal lobe (*x, y, z* = 12, −33, 59, *Z* = 5.19, P_{FDR} = 0.002), the anterior (*x, y, z* = 3, 34, 27, *Z* = 4.58, P_{FDR} = 0.002) and posterior cingulate (*x, y, z* = 8, −52, 15, *Z* = 4.82, P_{FDR} = 0.002, *R* = 0.96) and the precuneus on both sides (right: *x, y, z* = 11, −71, 51, *Z* = 5.44, P_{FDR} = 0.002; left: *x, y, z* = −8, −48, 49, *Z* = 4.96, P_{FDR} = 0.002) (Table 2, Fig. 4).

GAF

The GAF scores of our patients ranged from 30 to 100% with a mean of 61% (SD = 27.8) (Table 1). Correlating the morphometric data with the GAF score revealed a reduction of grey matter mostly in the middle frontal gyrus of the right frontal lobe (*x, y, z* = 30, 7, 49, *Z* = 5.47, P_{FDR} = 0.001), the precuneus (*x, y, z* = 11, −61, 56, *Z* = 6.02, P_{FDR} = 0.001; *R* = 0.98), cuneus (*x, y, z* = 5, −85, 2, *Z* = 5.02, P_{FDR} = 0.001), the nucleus accumbens (*x, y, z* = 11, 5, −13, *Z* = 4.57, P_{FDR} = 0.001) and the cerebellum posterior lobe, lobule VIII (*x, y, z* = −23, −65, −30, *Z* = 4.97, P_{FDR} = 0.001) (Table 2, Figs 3 and 4).

Disease duration

In order to investigate whether the SCA17 disease severity correlates with changes in grey matter volume, volumetric data were correlated with disease duration by simple

Table 2 Summary of significant grey matter decreases in SCA17

Region		Left hemisphere					Right hemisphere				
Lobes	Labels	Coordinates (mm)			*T*-value	*Z*-score	Coordinates (mm)			*T*-value	*Z*-score
		x	*y*	*z*			*x*	*y*	*z*		
1. Categorical comparison											
Cerebellum	Cerebellum posterior lobe (lobule VIII)	−15	−66	−45	11.48	6.48	13	−47	−53	5.19	4.15
Sublobar	Putamen	−20	17	−7	4.94	4.01	20	14	5	4.72	3.88
	Thalamus	−19	−32	10	3.74	3.25					
Frontal lobe	Inferior frontal gyrus	−41	38	4	5.63	4.39					
Parietal lobe	Inferior parietal lobule						63	−39	25	3.63	3.19
Occipital lobe	Cuneus	16	−101	1	4.10	3.49					
2. Clinical correlations											
(a) Ataxia											
Cerebellum	Cerebellum posterior lobe (lobule VIII)	−12	−65	−50	4.88	3.42	11	−74	−49	6.64	4.02
	Cerebellum posterior lobe (lobule VIII)	−22	−45	−53	4.40	3.21	15	−47	−53	4.43	3.20
(b) Spasticity											
Sublobar	Lentiform ncl. (putamen)	−21	12	−2	7.43	4.24	17	7	−13	9.98	4.80
(c) UPDRSIII											
Sublobar	Lentiform ncl. (putamen)	−21	6	4	8.43	4.48					
(d) MMSE											
Sublobar	Accumbens ncl.						11	6	−12	14.63	5.47
(e) F07											
Frontal lobe	Paracentral lobule						12	−33	59	12.45	5.19
	Medial frontal gyrus						2	41	24	8.46	4.49
	Middle frontal gyrus						29	51	4	9.70	4.74
Limbic lobe	Anterior cingulate						3	34	27	8.89	4.58
	Posterior cingulate						8	−52	15	10.11	4.82
Parietal lobe	Precuneus	−8	−48	49	10.91	4.96	11	−71	51	14.39	5.44
(f) GAF											
Frontal lobe	Middle frontal gyrus						30	7	49	15.47	5.47
							30	53	4	11.80	5.10
	Precentral gyrus	−43	−9	41	12.94	5.26					
Temporal lobe	Superior temporal gyrus	−66	−42	18	13.82	5.37					
Parietal lobe	Precuneus						11	−61	56	20.39	6.02
	Inferior parietal lobule						56	−47	21	11.31	5.02
Occipital lobe	Cuneus						5	−85	2	11.28	5.02
	Superior occipital gyrus	−35	−88	23	10.78	4.94					
Sublobar	Accumbens ncl.						11	5	−13	8.81	4.57
	Insula	−40	−8	−1	12.67	5.22					
Cerebellum	Cerebellum posterior lobe (lobule VIII)	−23	−65	−30	11.0	4.97					
(g) Disease duration											
Cerebellum	Cerebellum posterior lobe (lobule VIII)	−52	−58	−38	7.23	4.19	55	59	−28	5.19	3.53
	Cerebellum posterior lobe (crus I)	−49	−48	−36	8.72	4.54					
Sublobar	Accumbens ncl.	7	−3	−17	6.13	3.86	−8	−1	−17	5.55	3.67
	Lentiform ncl. (putamen)	16	5	−5	4.67	3.33					
Limbic lobe	Anterior cingulate	−1	24	41	8.12	4.41					
	Posterior cingulate	14	−63	10	10.23	4.84					
Frontal lobe	Middle frontal gyrus	−38	60	3	5.39	3.61	50	29	34	6.05	3.84
	Medial frontal gyrus	−3	−14	59	9.31	4.79	6	−16	60	13.20	5.30
Temporal lobe	Superior temporal gyrus						50	−2	−5	8.01	4.38
	Middle temporal gyrus	−52	−58	−38	7.23	4.19	57	−53	4	11.85	5.11
Occipital lobe	Cuneus	10	−90	6	10.35	4.86					

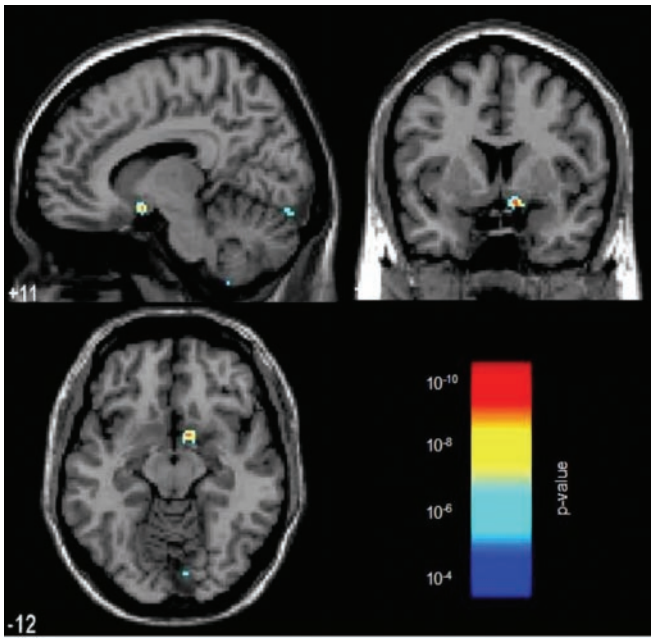

Fig. 2 Demonstration of the highly significant negative correlation between grey matter density in the nucleus accumbens on the right side and the MMSE (P_{FDR} = 0.01). The colour bar represents the *P* values.

regression analysis (mean = 10.92 years, SD = 7.91). This revealed the most prominent loss of grey matter volume in the cerebellum (*x, y, z* = −52, −58, −38, *Z* = 4.19, P_{FDR} = 0.002), the middle (*x, y, z* = 50, 29, 34, *Z* = 3.84, P_{FDR} = 0.002) and medial frontal gyrus (*x, y, z* = 6, −16, 60, *Z* = 5.30, P_{FDR} = 0.002), the superior (*x, y, z* = 50, −2, −5, *Z* = 4.38, P_{FDR} = 0.002) and middle temporal gyrus (*x, y, z* = 57, −53, 4, *Z* = 5.11, P_{FDR} = 0.002), the cuneus (*x, y, z* = 10, −90, 6, *Z* = 4.86, P_{FDR} = 0.002) and nucleus accumbens (*x, y, z* = 7, −3, 17, *Z* = 3.86, P_{FDR} = 0.002). Additionally, the basal ganglia, in particular the nucleus lentiformis (*x, y, z* = 16, 5, −5, *Z* = 3.33, P_{FDR} = 0.004) and limbic structures such as the anterior (*x, y, z* = −1, 24, 41, *Z* = 4.41, P_{FDR} = 0.002) and posterior cingulate (*x, y, z* = 14, −63, 10, *Z* = 4.84, P_{FDR} = 0.002) were affected (for details see Table 2).

Discussion

In this first systematic study of SCA17 patients employing VBM, we found a general pattern of atrophy characteristic for the main symptoms of this disease. Importantly, we also identified several more specific functional–morphological correlations including differential patterns of degeneration related to motor signs on the one hand and to neuropsychiatric signs on the other.

The categorical comparison between SCA17 patients and normal subjects mainly revealed a decrease of grey matter density that was centred around the mesial cerebellar structures, the rostral parts of the cerebrum and parts of the motor network. Furthermore, the correlations between the grey matter values and ataxia, spasticity, and UPDRS III scores revealed specific sites of degeneration in the cerebellum and cerebrum. The correlation of the morphometric data with neuropsychiatric scores, e.g. MMSE, personality change and GAF showed specific degeneration in cerebral structures that may stand for cognitive and emotional dysfunctions. Interestingly, all the areas with loss of grey matter seen in the categorical comparison as well as in the clinical correlations were also detected in the simple regression analysis with the duration of the SCA17 disease, highlighting the time dependency of the pathological changes.

One important result of the present study is the identification of a general pattern of atrophy of grey matter that was common in all patients, irrespective of the clinical status. This general pattern comprised mesial cerebellar structures, lesions in which are known to cause ataxia symptoms (Gilman, 1992). Furthermore, the basal ganglia were also significantly affected.

Additionally, decrease in grey matter density was also observed in rostral occipito-parietal structures as well as in parts of the motor network. These findings indicate specific atrophic changes reflecting the leading clinical features of SCA17 patients, cerebellar and extrapyramidal signs.

Similar findings such as cerebellar and to some extent putaminal atrophy, depending on the SCA mutation, were demonstrated in previous morphometric MRI studies in other subgroups of SCA, in particular in SCA1, SCA2 and SCA3 (Klockgether *et al.*, 1998). Furthermore, our data fit well with the few available morphometric and neuropathological data on SCA17: one previous MRI study showed diffuse cortical and cerebellar atrophy in SCA17 patients, that was accentuated in the cerebellum (Rolfs *et al.*, 2003), whereas another one found a mild atrophy of the cerebral cortex, the caudate nucleus and the cerebellum (Toyoshima *et al.*, 2004). Recently, the first case of SCA17 was described to have a putaminal rim hyperintensity on MRI, suggestive of basal ganglia dysfunction (Loy *et al.*, 2005). Metabolic basal ganglia dysfunction in SCA17 has also been reported, using striatal dopamine transporter and 18-fluorodeoxyglucose positron emission tomographic scanning (Gunther *et al.*, 2004).

Correspondingly, neuropathological findings in SCA17 revealed neuronal loss and gliosis in the Purkinje cell layer and in the basal ganglia (Bruni *et al.*, 2004; Toyoshima *et al.*, 2004).

Taken together, our morphometric data are comparable with previous published data of SCA17 patients concerning cerebellar and extrapyramidal degeneration patterns.

To date, however, no attempts have been made to identify a more specific morphometric correlate of the various neurological and psychiatric symptoms characteristic of SCA17.

One new feature of our study, compared to previous ones, was the calculation of a simple regression analysis between dedicated clinical scores and grey matter morphometry.

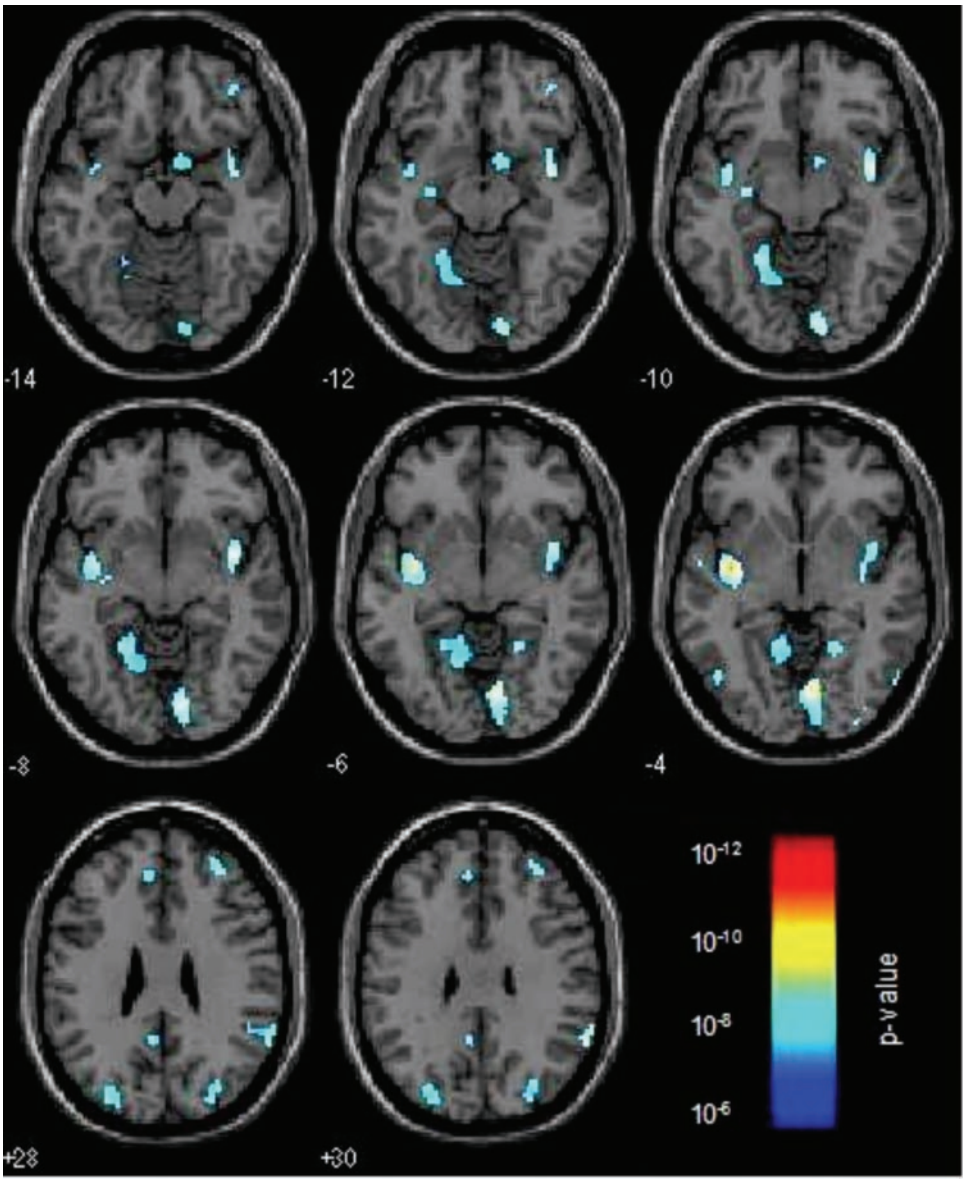

Fig. 3 Visualization of the relationship between the decreased grey matter and the severity of the GAF (P_{FDR} = 0.001). The data demonstrate a GAF-correlated reduction of grey matter in the right frontal lobe, the precuneus, the cuneus, the nucleus accumbens, the parieto-occiptal junction on the both sides and the insula on the left side. The colour bar represents the *P* values.

Correlation between grey matter degeneration and motor scales

The pathognomonical feature of SCA17 patients—cerebellar ataxia—results to a large extent from degeneration of the cerebellum and its afferent and efferent connections (Klockgether *et al.*, 1998). As expected, the correlation between the individual values of the ICARS in our 12 SCA17 patients and their morphometric data revealed a strong negative correlation with cerebellar structures. The severity of the clinical signs correlated with the extent of cerebellar atrophy. Accordingly, in a volumetric MRI analysis study, it was shown that the severity of cerebellar ataxia was inversely correlated with the cerebellar volume in patients with cerebellar degeneration (Richter *et al.*, 2005). Thus, decreased cerebellar volume seems to be quantitatively associated with the lack of harmonic and coordinated motion sequence.

In addition to cerebellar ataxia, other prominent non-cerebellar motor signs are present in SCA17 including spasticity (Hagenah *et al.*, 2004; Koide *et al.*, 1999), dystonia (Grundmann *et al.*, 2004; Hagenah *et al.*, 2004) and parkinsonism (Zuhlke *et al.*, 2001; Hernandez *et al.*, 2003; Rolfs *et al.*, 2003). In our study, correlation studies of VBM data with a spasticity score and the UPDRS III score revealed a negative correlation with putaminal volume. The putamen as part of the corpus striatum constitutes a fundamental part of the extrapyramidal motor system. Therefore, the local

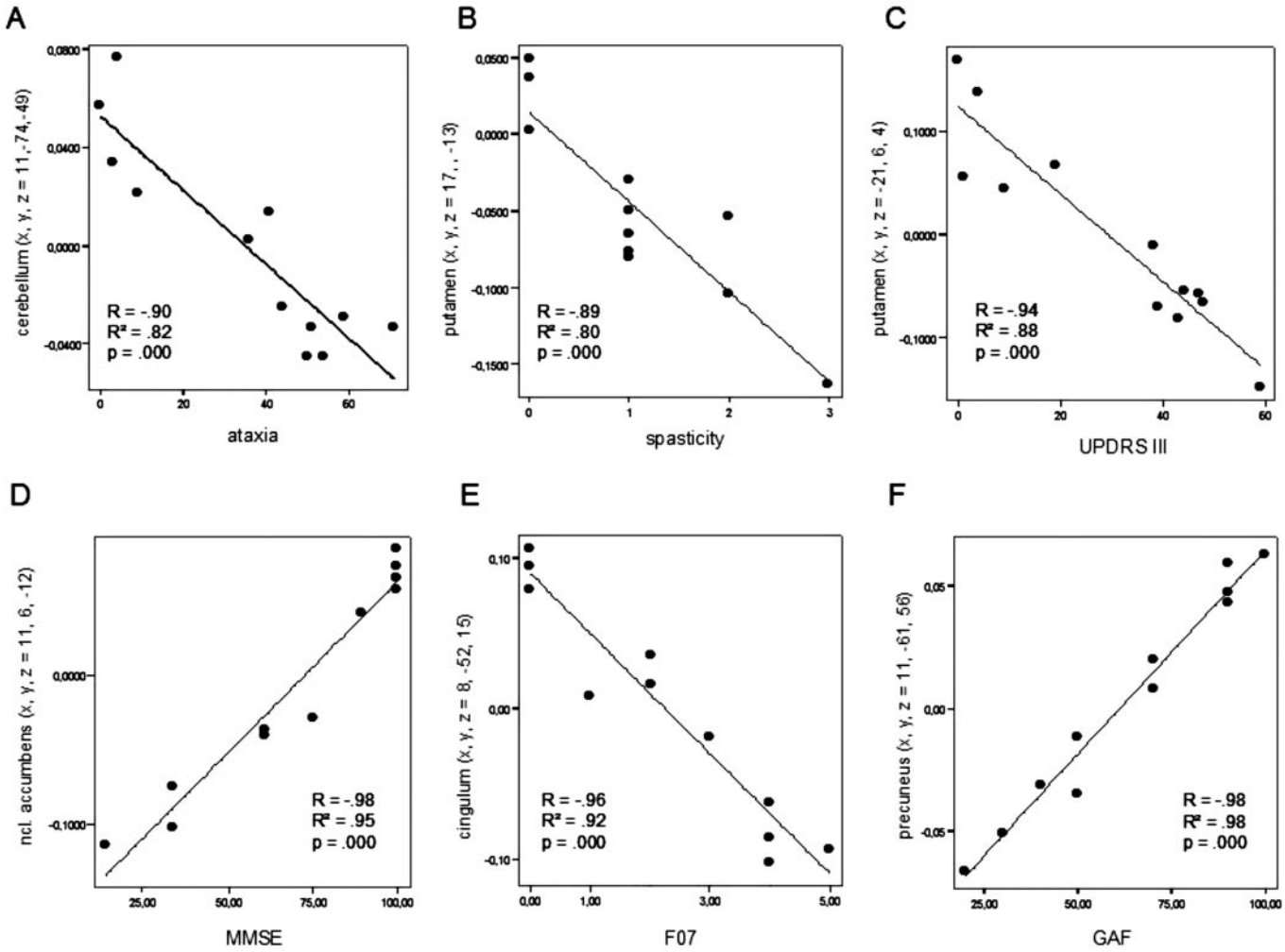

Fig. 4 Correlation of clinical parameters with morphometric data concerning characteristic areas. (**A**) Negative correlation between the ataxia score and atrophy of the right cerebellum (*x, y, z* = 11, −74, −49; *R* = −0.75); (**B**) negative correlation between the spasticity score and atrophy of the right putamen (*x, y, z* = 17, 7 −13; *R* = −0.89); (**C**) negative correlation between the UPDRS III and atrophy of the left putamen (*x, y, z* = −21, 6, 4; *R* = −0.71); (**D**) positive correlation between the MMSE and the atrophy of the right nucleus accumbens (*x, y, z* = 11, 6, −12; *R* = 0.98); (**E**) negative correlation between F07 and exemplary atrophy of the right cingulum (*x, y, z* = 8, −52, 15; *R* = −0.96); (**F**) positive correlation between GAF and atrophy of the right precuneus (*x, y, z* = 11, −61, 56; *R* = 0.98).

degenerations may reflect the severity of clinical extrapyramidal signs. As mentioned before, basal ganglia dysfunction was recently suspected in an MRI study of SCA17 showing a putaminal rim hyperintensity on T2-weighted MRI (Loy *et al.*, 2005). This was additionally observed in a functional imaging study using striatal dopamine transporter (DAT) and striatal dopamine D_2 receptor (D_2R) binding as well as measurement of glucose metabolism (Gunther *et al.*, 2004). Interestingly, a marked reduction of DAT availability was reported upon follow-up comparable to Parkinson's disease (Chouker *et al.*, 2001; Gunther *et al.*, 2004). Besides, a post mortem examination of SCA17 patients showed not only cortical, subcortical and cerebellar atrophy but also a nerve cell loss in the striatum that was one of the neuropathological characteristics of the autopsy (Bruni *et al.*, 2004).

In accordance with previously published data, we showed that the extrapyramidal motor system is also affected and that the severity of symptoms correlates with the decrease of putaminal grey matter in SCA17.

Correlation between grey matter degeneration and neuropsychiatric scales

In our SCA17 patient group a high rate of dementia (50%) was found. The occurrence of dementia in patients with SCA17 has been described previously (Hernandez *et al.*, 2003; Rolfs *et al.*, 2003; De Michele *et al.*, 2003). Thus, in 5–25% of SCA1 patients of Spanish descent mild mental deterioration (Burk *et al.*, 2003) and 'frontal-like symptoms' such as euphoria and emotional instability were described (Genis *et al.*, 1995). In clinical descriptions of SCA2, the

frequency of cognitive deficits varies between 5 and 19% (Durr *et al.*, 1995; Burk *et al.*, 1997; Cancel *et al.*, 1997; Wadia, 1984), whereas SCA3 individuals did not show cognitive dysfunction (Rosenberg *et al.*, 1976; Coutinho and Andrade, 1978; Fowler, 1984; Burt *et al.*, 1993). Mild deficits of verbal memory were found in SCA1, SCA2 and SCA3 (Burk *et al.*, 2003). It has even been postulated, that initial presenile dementia with behavioural symptoms should be added to the 'conventional' symptoms (Bruni *et al.*, 2004).

'Cognitive affective syndromes' have been described in cerebellar patients, showing specific core features, such as executive spatial, linguistic and affective signs and 'non-specific' dementia (Schmahmann and Sherman, 1998). Patients of the aforementioned study suffered from infarcts in different regions, cerebellar atrophies and post-infectious cerebellitis. In our study, we focused on psychiatric disorders and dementia in SCA17. Further studies might reveal more complex correlations of neuropsychological deficits with reduced brain volume.

Our data demonstrate for the first time that the intellectual decline reflected by a reduction of the MMSE score was significantly associated with a reduction of the nucleus accumbens volume on the right side. Recently, a reduction of grey matter volume of the nucleus accumbens has been found in a VBM study in Parkinson's disease (PD) with dementia compared to healthy controls (Summerfield *et al.*, 2005); therefore, this structure may play a seminal role in the development of dementia in neurodegenerative diseases.

The nucleus accumbens, belonging to the ventral striatum, is often described as one part of a cortico-striato-thalamo-cortical loop. Compared to other striatal pathways, the nucleus accumbens receives especially intense afferent projections from the limbic system. Major inputs to the nucleus accumbens include the prefrontal cortex and dopaminergic neurons located in the ventral tegmental area which are connected via the mesolimbic pathway (Christakou *et al.*, 2004; Morgane *et al.*, 2005; Phan *et al.*, 2005). The nucleus accumbens can therefore be interpreted as a 'relay-station' being responsible for the transition from 'motivation to action' or 'emotion to locomotion'. The finding of a significant correlation between cognitive decline and reduced nucleus accumbens volume may therefore reflect the reduced capability of emotional and behavioural control, as observed in SCA17 patients suffering from dementia.

We found a high rate of definite personality changes probably due to the brain disease in SCA17 (42%). When SCA17 patients with a diagnosis of probable or possible personality change are included as many as 75% may be considered as affected (two or one F07 criteria fulfilled). To our knowledge, this aspect has not been addressed before in SCA17. A rate of personality change of 26% was observed in patients with degenerative cerebellar disease including SCA1–SCA3 and SCA6–SCA8 corresponding to a rate of 48% in Huntington's disease (Leroi *et al.*, 2002). Although the diagnosis of a personality change was made independently of the diagnosis of dementia or cognitive impairment, all patients with a personality change had an MMSE score of <80%. In the patients with a possible or probable personality change one patient also had dementia and another one showed a cognitive decline, whereas other comorbidities were agoraphobia, social phobia and adjustment disorders. In the above-mentioned study (Leroi *et al.*, 2002), a rate of 19% of demented or cognitively mildly impaired patients with degenerative cerebellar disease was observed but the authors did not investigate the possible association between cognitive decline and personality change in these patients.

In the present study, the degree of personality changes due to the brain dysfunction in SCA17 correlates highly with brain volume reductions in a wide range of cortical areas including frontal, parietal (precuneus) and limbic (anterior and posterior cingulate) structures. It is well accepted that the frontal and the limbic systems represent the main neuroanatomical basis of the emotional system (Heinzel *et al.*, 2005). Emotional processes are assumed to derive from basic drives that appear to be centred in the limbic system, whereas frontal areas are assumed to be responsible for control of these emotional drives. The anterior cingulate as well as the precuneus have been shown to be involved in attentional, motivational and emotional processing (Davis *et al.*, 2005). Thus, a dysfunction within this circuit may explain a reduced ability to persevere with goal-directed activities and increased emotional liability or irritability as we observed in most of our patients with a personality change. The observation of disinhibited expression of needs or impulses on the one hand and/or apathy on the other may reflect the frontal dysfunctions. Interestingly, the loss of grey matter in the mesial-frontal and parietal cortical structures was most prominent in the correlation with the duration of disease. This finding confirms the conjecture that the extent of dysexecutive and attentional deficits increases with the progress of the disease over time.

A significant grey matter reduction has also been found at the parietal occipital junction (IPTO), in a region that may include the visual area V3A (Essen and Zeki, 1978; Culham and Kanwisher, 2001). In previous neuroimaging studies, it has been shown that this area participates in attentional tasks (Corbetta *et al.*, 1998). The involvement of this area together with other prefrontal areas may explain the observed attentional dysfunctions of our SCA17 patients.

A remarkable overlap between SCA17 phenotypes and Huntington's disease-like phenotypes was described (Bauer *et al.*, 2004). As the major cause of Huntington's disease, a CAG-repeat expansion was identified in the *Huntingtin* gene resulting in an expanded polyglutamine chain in the huntingtin protein (The huntington's Collaboration Research Group, 1993). Similar to our observation in SCA17 patients, increased rates of cognitive impairment as well as personality change have also been reported in patients with Huntington's disease (Leroi *et al.*, 2002). Furthermore, alterations of the same cerebral and cerebellar structures have been observed in both patient groups, suggesting that there

may be a pathophysiological overlap between both of these CAG-repeat diseases (Thieben *et al.*, 2002; Rosas *et al.*, 2003; Kassubek *et al.*, 2004).

Reflecting the general functional impairment in daily life due to psychiatric disease, the GAF measures the disturbance of executive functions affecting social, occupational and psychological behaviour. We found that a GAF-score reduction correlated significantly with a degeneration not only of the structures that were associated with a cognitive decline (nucleus accumbens) or a personality change (frontal areas and the precuneus), but also in cerebellar areas. This finding underlines the notion that the primary degeneration of cerebellar structures, as hypothesized in SCA, has an important impact also on cerebral structures and their function. Pathophysiologically, anatomical evidence was found that prefrontal association areas are tightly linked to the cerebellum via pontine structures (Allen and Tsukahara, 1974; Schmahmann and Pandya, 1995, 1997), while efferent connections arising from the dentate nucleus and projecting to the prefrontal cortex represent the feedback limb of this cerebrocerebellar circuitry (Middleton and Strick, 1994, 1997; Schmahmann and Sherman, 1997). The wide range of psychiatric signs observed in SCA17 patients may therefore be explained by dysfunctions within this cerebrocerebellar network.

In summary, the combination of modern magnetic resonance morphometric techniques with a thorough and quantitative clinical investigation of patients provides a powerful tool for getting a better understanding of the pathophysiological basis of neurodegenerative diseases. However, further longitudinal studies using VBM and other morphometric techniques are needed to get a deeper insight into the dynamic development of the disease.

Acknowledgements

This work was supported by intramural grants from the Medical Faculty, University of Luebeck to K.L. and C.K. F.B. and C.K. are supported by the Volkswagen Stiftung. NeuroImage Nord is supported by structural grants from the DFG and BMBF (01GO0207). We thank Heather Boston, Anja Hiller and Adam McNamara for their valuable comments.

References

Allen GI, Tsukahara N. Cerebrocerebellar communication systems. Physiol Rev 1974; 54: 957–1006.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 4th edn. Washington (DC): American Psychiatric Association; 1994.

Ashburner J, Friston KJ. Nonlinear spatial normalization using basis functions. Hum Brain Mapp 1999; 7: 254–66.

Bang OY, Lee PH, Kim SY, Kim HJ, Huh K. Pontine atrophy precedes cerebellar degeneration in spinocerebellar ataxia 7: MRI-based volumetric analysis. J Neurol Neurosurg Psychiatry 2004; 75: 1452–6.

Bauer P, Laccone F, Rolfs A, Wullner U, Bosch S, Peters H, et al. Trinucleotide repeat expansion in SCA17/TBP in white patients with Huntington's disease-like phenotype. J Med Genet 2004; 41: 230–2.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Stat Soc Ser B 2000; 57: 289–300.

Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1986; 67: 206–7.

Bruni AC, Takahashi-Fujigasaki J, Maltecca F, Foncin JF, Servadio A, Casari G, et al. Behavioral disorder, dementia, ataxia, and rigidity in a large family with TATA box-binding protein mutation. Arch Neurol 2004; 61: 1314–20.

Burk K, Stevanin G, Didierjean O, Cancel G, Trottier Y, Skalej M, et al. Clinical and genetic analysis of three German kindreds with autosomal dominant cerebellar ataxia type I linked to the SCA2 locus. J Neurol 1997; 244: 256–61.

Burk K, Globas C, Bosch S, Klockgether T, Zuhlke C, Daum I, et al. Cognitive deficits in spinocerebellar ataxia type 1, 2, and 3. J Neurol 2003; 250: 207–11.

Burt T, Blumbergs P, Currie BA. Dominant hereditary ataxia resembling Machado-Joseph disease in Arnhem Land, Australia. Neurology 1993; 43: 1750–2.

Cancel G, Durr A, Didierjean O, Imbert G, Burk K, Lezin A, et al. Molecular and clinical correlations in spinocerebellar ataxia 2: a study of 32 families. Hum Mol Genet 1997; 6: 709–15.

Chouker M, Tatsch K, Linke R, Pogarell O, Hahn K, Schwarz J. Striatal dopamine transporter binding in early to moderately advanced Parkinson's disease: monitoring of disease progression over 2 years. Nucl Med Commun 2001; 22: 721–5.

Christakou A, Robbins TW, Everitt BJ. Prefrontal cortical-ventral striatal interactions involved in affective modulation of attentional performance: implications for corticostriatal circuit function. J Neurosci 2004; 24: 773–80.

Corbetta M, Akbudak E, Conturo TE, Snyder AZ, Ollinger JM, Drury HA, et al. A common network of functional areas for attention and eye movements. Neuron 1998; 21: 761–73.

Coutinho P, Andrade C. Autosomal dominant system degeneration in Portuguese families of the Azores Islands. A new genetic disorder involving cerebellar, pyramidal, extrapyramidal and spinal cord motor functions. Neurology 1978; 28: 703–9.

Culham JC, Kanwisher NG. Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol 2001; 11: 157–63.

Davis KD, Taylor KS, Hutchison WD, Dostrovsky JO, McAndrews MP, Richter EO, et al. Human anterior cingulate cortex neurons encode cognitive and emotional demands. J Neurosci 2005; 25: 8402–6.

De Michele G, Maltecca F, Carella M, Volpe G, Orio M, De Falco A, et al. Dementia, ataxia, extrapyramidal features, and epilepsy: phenotype spectrum in two Italian families with spinocerebellar ataxia type 17. Neurol Sci 2003; 24: 166–7.

Durr A, Smadja D, Cancel G, Lezin A, Stevanin G, Mikol J, et al. Autosomal dominant cerebellar ataxia type I in Martinique (French West Indies). Clinical and neuropathological analysis of 53 patients from three unrelated SCA2 families. Brain 1995; 118: 1573–81.

Essen DC, Zeki SM. The topographic organization of rhesus monkey prestriate cortex. J Physiol 1978; 277: 193–226.

Fahn S, Elton R. Unified Parkinson's Disease Rating Scale. Recent developments in Parkinson's disease. London: Macmillan Health Care Information; 1987. p. 153–64.

Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Fowler HL. Machado-Joseph-Azorean disease. A ten-year study. Arch Neurol 1984; 41: 921–5.

Genis D, Matilla T, Volpini V, Rosell J, Davalos A, Ferrer I, et al. Clinical, neuropathologic, and genetic studies of a large spinocerebellar ataxia type 1 (SCA1) kindred: (CAG)n expansion and early premonitory signs and symptoms. Neurology 1995; 45: 24–30.

Gilman S. Cerebellum and motor dysfunction. Philadelphia: W.B. Saunders Company; 1992.

Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain

structure: a voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage 2001a; 14: 685–700.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001b; 14: 21–36.

Grundmann K, Laubis-Herrmann U, Dressler D, Vollmer-Haase J, Bauer P, Stuhrmann M, et al. Mutation at the SCA17 locus is not a common cause of primary dystonia. J Neurol 2004; 251: 1232–4.

Gunther P, Storch A, Schwarz J, Sabri O, Steinbach P, Wagner A, et al. Basal ganglia involvement of a patient with SCA17—a new form of autosomal dominant spinocerebellar ataxia. J Neurol 2004; 251: 896–7.

Hagenah JM, Zuhlke C, Hellenbroich Y, Heide W, Klein C. Focal dystonia as a presenting sign of spinocerebellar ataxia 17. Mov Disord 2004; 19: 217–20.

Heinzel A, Bermpohl F, Niese R, Pfennig A, Pascual-Leone A, Schlaug G, et al. How do we modulate our emotions? Parametric fMRI reveals cortical midline structures as regions specifically involved in the processing of emotional valences. Brain Res Cogn Brain Res 2005; 25: 348–58.

Hellier P, Barillot C, Corouge I, Gibaud B, Le Goualher G, Collins DL, et al. Retrospective evaluation of intersubject brain registration. IEEE Trans Med Imaging 2003; 22: 1120–30.

Hernandez D, Hanson M, Singleton A, Gwinn-Hardy K, Freeman J, Ravina B, et al. Mutation at the SCA17 locus is not a common cause of parkinsonism. Parkinsonism Relat Disord 2003; 9: 317–20.

Kassubek J, Juengling FD, Kioschies T, Henkel K, Karitzky J, Kramer B, et al. Topography of cerebral atrophy in early Huntington's disease: a voxel based morphometric MRI study. J Neurol Neurosurg Psychiatry 2004; 75: 213–20.

Klockgether T, Skalej M, Wedekind D, Luft AR, Welte D, Schulz JB, et al. Autosomal dominant cerebellar ataxia type I. MRI-based volumetry of posterior fossa structures and basal ganglia in spinocerebellar ataxia types 1, 2 and 3. Brain 1998; 121: 1687–93.

Koide R, Kobayashi S, Shimohata T, Ikeuchi T, Maruyama M, Saito M, et al. A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: a new polyglutamine disease? Hum Mol Genet 1999; 8: 2047–53.

Leroi I, O'Hearn E, Marsh L, Lyketsos CG, Rosenblatt A, Ross CA, et al. Psychopathology in patients with degenerative cerebellar diseases: a comparison to Huntington's disease. Am J Psychiatry 2002; 159: 1306–14.

Loy CT, Sweeney MG, Davis MB, Wills AJ, Sawle GV, Lees AJ, et al. Spinocerebellar ataxia type 17: extension of phenotype with putaminal rim hyperintensity on magnetic resonance imaging. Mov Disord 2005; 20: 1521–3.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 2003; 19: 1233–9.

Maltecca F, Filla A, Castaldo I, Coppola G, Fragassi NA, Carella M, et al. Intergenerational instability and marked anticipation in SCA-17. Neurology 2003; 61: 1441–3.

Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). Cerebellum 2005; 4: 2–6.

Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science 1994; 266: 458–61.

Middleton FA, Strick PL. Dentate output channels: motor and cognitive components. Prog Brain Res 1997; 114: 553–66.

Morgane PJ, Galler JR, Mokler DJ. A review of systems and networks of the limbic forebrain/limbic midbrain. Prog Neurobiol 2005; 75: 143–60.

Murata Y, Kawakami H, Yamaguchi S, Nishimura M, Kohriyama T, Ishizaki F, et al. Characteristic magnetic resonance imaging findings in spinocerebellar ataxia 6. Arch Neurol 1998; 55: 1348–52.

Nakamura K, Jeong SY, Uchihara T, Anno M, Nagashima K, Nagashima T, et al. SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein. Hum Mol Genet 2001; 10: 1441–8.

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry 2005; 57: 210–9.

Richter S, Dimitrova A, Maschke M, Gizewski E, Beck A, Aurich V, et al. Degree of cerebellar ataxia correlates with three-dimensional MRI-based cerebellar volume in pure cerebellar degeneration. Eur Neurol 2005; 54: 23–7.

Rolfs A, Koeppen AH, Bauer I, Bauer P, Buhlmann S, Topka H, et al. Clinical features and neuropathology of autosomal dominant spinocerebellar ataxia (SCA17). Ann Neurol 2003; 54: 367–75.

Rosas HD, Koroshetz WJ, Chen YI, Skeuse C, Vangel M, Cudkowicz ME, et al. Evidence for more widespread cerebral pathology in early HD: an MRI-based morphometric analysis. Neurology 2003; 60: 1615–20.

Rosenberg RN, Nyhan WL, Bay C, Shore P. Autosomal dominant striatonigral degeneration. A clinical, pathologic, and biochemical study of a new genetic disorder. Neurology 1976; 26: 703–14.

Schmahmann JD, Pandya DN. Prefrontal cortex projections to the basilar pons in rhesus monkey: implications for the cerebellar contribution to higher function. Neurosci Lett 1995; 199: 175–8.

Schmahmann JD, Pandya DN. Anatomic organization of the basilar pontine projections from prefrontal cortices in rhesus monkey. J Neurosci 1997; 17: 438–58.

Schmahmann JD, Sherman JC. Cerebellar cognitive affective syndrome. Int Rev Neurobiol 1997; 41: 433–40.

Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121: 561–79.

Schmahmann JD, Doyon J, Toga AW, Terides M, Evans AC. MRI atlas of the human cerebellum. San Diego, CA: Academic Press; 2000.

Stevanin G, Fujigasaki H, Lebre AS, Camuzat A, Jeannequin C, Dode C, et al. Huntington's disease-like phenotype due to trinucleotide repeat expansions in the TBP and JPH3 genes. Brain 2003; 126: 1599–603.

Summerfield C, Junque C, Tolosa E, Salgado-Pineda P, Gomez-Anson B, Marti MJ, et al. Structural brain changes in Parkinson disease with dementia: a voxel-based morphometry study. Arch Neurol 2005; 62: 281–5.

The Huntington's Collaboration Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72: 971–83.

Thieben MJ, Duggins AJ, Good CD, Gomes L, Mahant N, Richards F, et al. The distribution of structural neuropathology in pre-clinical Huntington's disease. Brain 2002; 125: 1815–28.

Toyoshima Y, Yamada M, Onodera O, Shimohata M, Inenaga C, Fujita N, et al. SCA17 homozygote showing Huntington's disease-like phenotype. Ann Neurol 2004; 55: 281–6.

Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, et al. International cooperative ataxia rating scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci 1997; 145: 205–11.

Wadia NH. A variety of olivopontocerebellar atrophy distinguished by slow eye movements and peripheral neuropathy. Adv Neurol 1984; 41: 149–77.

World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1992.

Yu GY, Howell MJ, Roller MJ, Xie TD, Gomez CM. Spinocerebellar ataxia type 26 maps to chromosome 19p13.3 adjacent to SCA6. Ann Neurol 2005; 57: 349–54.

Zuhlke C, Hellenbroich Y, Dalski A, Kononowa N, Hagenah J, Vieregge P, et al. Different types of repeat expansion in the TATA-binding protein gene are associated with a new form of inherited ataxia. Eur J Hum Genet 2001; 9: 160–4.