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Evidence for a direct association between cortical atrophy and cognitive impairment in relapsing–remitting MS

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Cognitive deficits affecting memory, attention and speed of information processing are common in multiple sclerosis (MS). The mechanisms of cognitive impairment remain unclear. Here, we examined the association between neuropsychological test performance and brain atrophy in a group of mildly disabled patients with relapsing–remitting MS. We applied voxel-based morphometry (SPM2) to investigate the distribution of brain atrophy in relation to cognitive performance. Patients had lower scores than control subjects on tests of memory and executive function, including the PASAT, Digit Span Backward and a test of short-term verbal memory (Memo). Among patients, but not healthy controls, performance on the PASAT, a comprehensive measure of cognitive function and reference task for the cognitive evaluation of MS-patients, correlated with global grey matter volume as well as with grey matter volume in regions associated with working memory and executive function, including bilateral prefrontal cortex, precentral gyrus and superior parietal cortex as well as right cerebellum. Compared to healthy subjects, patients showed a volume reduction in left temporal and prefrontal cortex, recently identified as areas predominantly affected by diffuse brain atrophy in MS. A comparison of low performers in the patient group with their matched control subjects showed more extensive and bilateral temporal and frontal volume reductions as well as bilateral parietal volume loss, compatible with the progression of atrophy found in more advanced MS-patients. These findings indicate that MS-related deficits in cognition are closely associated with cortical atrophy.

Introduction

Cognitive impairment in multiple sclerosis, an immune-mediated disease of the central nervous system, affects approximately 40–70% of patients (Amato et al., 2001; Rao et al., 1991) and typically involves memory, attention and speed of information processing (Amato et al., 2001; Grafman et al., 1991; Litvan et al., 1988; Rao et al., 1991). Deficits of cognition in MS have been attributed to slowed neural conduction resulting from white matter (WM) pathology (Arnett et al., 1994; Rao et al., 1989; Swirsky-Sacchetti et al., 1992). But correlations between cognitive status and WM lesion load on T2-weighted MRI or microscopic tissue damage measured with magnetization transfer imaging (MTI) and magnetic resonance spectroscopy have been modest (Franklin et al., 1988; Foong et al., 1999; Huber et al., 1992; Rao et al., 1989; Rovaris and Filippi, 2000; Swirsky-Sacchetti et al., 1992). More recently, grey matter (GM) pathology has been identified as a significant substrate of cognitive impairment (Amato et al., 2004; Benedict et al., 2004; Zivadinov et al., 2001). Cortical atrophy occurs early in the disease (Chard et al., 2002; De Stefano et al., 2003; Zivadinov et al., 2001) and appears to be more closely linked to cognitive decline than changes in WM (Amato et al., 2004; Benedict et al., 2004; Zivadinov et al., 2001). Here, we investigated the association between cognitive performance and brain volume in a group of patients with clinically early relapsing–remitting MS and in a group of healthy control subjects with voxel-based morphometry (VBM), an unbiased method of regional volume analysis.

Methods

Subjects

Nineteen patients with definite multiple sclerosis (McDonald et al., 2001) between the ages of 22 and 46 years (mean age 32.4 ±

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8.2 years) and 19 age- and gender-matched healthy volunteers (mean age 31.7 ± 7.5 years, range 22 to 44 years), participated in the study. All subjects had graduated from high school; 15 patients and 16 healthy subjects had a college-level education. Clinical evaluation of patients included complete neurological examination and determination of Expanded Disability Status Scale (EDSS, Kurtzke, 1983). Inclusion criteria were a relapsing–remitting course of disease and an EDSS score <4.0. Median EDSS was 1.0 (range 0–3.5), median duration of disease since diagnosis 13 months (range 2–60 months) and median WM lesion load 0.46 cm^3 (range 0.04–5.52 cm^3, Table 1). Patients had not suffered a relapse or taken steroids within the preceding month and were not undergoing immunomodulatory treatment; they were examined before beginning such therapy or had decided against it. The study was approved by the clinical Institutional Review Board of Giessen University. All subjects gave informed consent.

Neuropsychological assessment

Memory functions were tested with the Digit Span and Digit span Backward (both HAWIE-R, Tewes, 1991), the Memo-test (Schaaf et al., 1994) and the paced auditory serial addition task (PASAT (Gronwall, 1977)). The Digit span and Memo tests are sensitive to deficits of short-term memory. The Digit Span Backward and PASAT require additional manipulation of encoded material and thus test for working memory. The PASAT also assesses divided attention and, as a result of the timing constraint, speed of information processing. During task performance, single digits are presented at regular intervals and the patient must add each new digit to the one immediately preceding it. The PASAT was presented at two levels of difficulty, using interstimulus intervals of 2.4 and 1.2 s. Normal attention functions were examined with tests of alertness, selective attention, and divided attention (TAP; Zimmermann and Fimm, 1993). Intelligence was screened with the multiple choice vocabulary test (MWT), a German test of verbal intelligence (Lehrl et al., 1995). Depression was assessed with the Beck Depression Inventory (Hautzinger, 1991). Group differences were assessed with the Wilcoxon matched pairs test and considered statistically significant if $P < 0.05$.

Structural image analysis

MRI examinations were performed on a 1.5 T whole body unit (Siemens Symphony with a quantum gradient system, Erlangen, Germany) using a standard head coil. They consisted of axial oblique proton density/T2-weighted (dual echo TE 13/91 ms and TR 3400 ms, 3 mm × 40 slices, matrix 250 × 100) and 3D high resolution T1-weighted images (MPRAGE, TE 4.18 ms, TR 1900 ms, flip angle 15 degrees, 1.0 mm × 160 slices, matrix 192 × 100). Data were acquired using contiguous interleaved slices.

White matter lesion load

WM lesion load was calculated from T2-weighted and proton density (PD) images by a single observer unaware of the patients' identity using a semi-automated segmentation technique based on a fuzzy c-means algorithm (MIPAV Version 1.22, Center for Information Technology, National Institutes of Health, Bethesda, MD). Total lesion volumes were reproducible in serial measurements to 7.1%.

Brain volume

Analysis of regional brain volume distribution. Brain volume was estimated for each subject with high-resolution T1-weighted images according to the method for VBM described by Good et al. (2001) with SPM2 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK, http//www.fil.ion.ucl.ac.uk/spm) and Matlab 6.5 software (The Mathworks, MA, USA). Briefly, this method involves an initial segmentation of T1-weighted MRI into GM and WM images in native space, followed

Table 1
Patient characteristics

Patient	Age (in years)	Duration of disease since diagnosis (in mo.)	EDSS	PASAT score	WM lesion load (in cm^3)	Probability measure of GM volume[a]	Probability measure of WM volume[a]
1	36	31	0	26	0.16	6.57×10^5	4.62×10^5
2	24	2	2	49	1.73	6.95×10^5	4.00×10^5
3	40	12	2	28	0.46	6.79×10^5	4.29×10^5
4	38	12	1	28	0.37	6.28×10^5	4.25×10^5
5	32	25	3.5	38	1.22	7.15×10^5	4.61×10^5
6	22	29	1	38	0.10	7.00×10^5	4.97×10^5
7	37	13	2.5	27	0.99	7.25×10^5	4.79×10^5
8	42	13	1	37	0.04	7.16×10^5	4.86×10^5
9	46	2	2	31	1.01	6.13×10^5	3.85×10^5
10	35	29	1	47	0.16	7.23×10^5	4.82×10^5
11	44	60	3	22	0.72	6.48×10^5	3.94×10^5
12	25	9	1	46	0.42	7.91×10^5	4.87×10^5
13	44	30	2.5	25	1.09	6.99×10^5	4.33×10^5
14	28	9	0	43	2.90	6.28×10^5	4.04×10^5
15	26	6	1.5	49	5.52	7.18×10^5	4.18×10^5
16	36	60	3.5	25	2.28	6.24×10^5	3.94×10^5
17	22	20	0	27	0.06	7.04×10^5	4.53×10^5
18	24	2	0	27	0.44	6.96×10^5	4.18×10^5
19	25	14	1	56	3.03	7.20×10^5	3.98×10^5
Median	32	13	1.0	31	0.46	6.99×10^5	4.33×10^5
	(22–46)	(2–60)	(0.0–3.5)	(22–56)	(0.04–5.52)	($6.13–7.91 \times 10^5$)	($3.94–4.97 \times 10^5$)

[a] Measures of GM and WM volume were derived from probability values for individual voxels (range 0–1) and number of voxels and thus lack units.

by a normalization of the GM and WM images to GM and WM templates in stereotactic space. To improve segmentation, the normalization parameters obtained from the nonlinear normalization of the GM and WM images are re-applied to the original whole-brain MRI and the normalized whole-brain MRI is then segmented into WM and GM images in a second segmentation step. Regional volume changes resulting from nonlinear normalization are corrected for by a multiplication of voxel values with Jacobean determinants derived from the nonlinear normalization. GM and WM images were then smoothed with a 12-mm FWHM kernel. We performed voxel-level random-effects analyses of group differences (paired t tests) and correlations between GM or WM volume and PASAT performance with SPM2.

Analysis of global GM/WM volume. For an estimation of global GM and WM volumes, number and mean intensity of voxels in the unsmoothed GM or WM images were multiplied. In order to analyze whether WM lesion volume was associated with diffuse WM atrophy (rather than with focal WM volume loss due to lesions), we replaced lesion voxels in WM with adjacent normal appearing white matter (NAWM) voxels. By replacing WM lesion voxels with NAWM voxels, we also compensated for the fact that the segmentation process involved in optimized VBM does not classify voxels as lesions. In order to substitute NAWM voxels for lesions voxels, lesions identified with the fuzzy c-means algorithm on PD/T2-weighted MRI were saved as a binary lesion map. The PD/T2-weighted images were then normalized to stereotactic space with SPM2 and the transformation matrix obtained from spatial normalization was applied to the lesion map. Subsequently, lesions in the normalized lesion map were saved as volumes of interest (VOI) and these VOI projected onto the WM probability map, their volume calculated (number of voxels × mean intensity), the VOI shifted to adjacent NAWM (horizontally or vertically, depending on where a sufficient area of NAWM could be found; a sufficient area was defined as the lesion area surrounded by a NAWM margin of at least 2 voxels; lesions on the border of WM/GM were moved along the WM/GM border, until a 2-voxel-margin around the remaining periphery of the lesion was established), their volume re-calculated and the original lesion volume replaced with the NAWM volume. The same procedure was performed with the GM probability map in order to eliminate voxels within lesions falsely attributed to GM. Group differences in brain volume were tested with the Wilcoxon matched pairs test at $P < 0.05$. Correlations between MR-measures of disease severity (GM-volume, WM-volume, WM lesion volume), neuropsychological performance and EDSS were analyzed with Spearman rank correlation tests and considered significant at $P < 0.05$.

Results

Performance on neuropsychological test battery

Patients obtained lower scores than healthy control subjects on both runs of the PASAT (2.4 and 1.2 s stimuli presentation intervals, $P < 0.05$). The group difference in mean performance and the range of scores within the patient group were greater for the more difficult version of the task with 1.2 s stimulus presentation intervals than for the test version with 2.4 s intervals (1.2 s interval: 35.2 ± 10.4 in patient group [range 22–56] vs. 42.5 ± 8.5 in control group [range 27–59]; 2.4 s interval: mean of 46.9 ± 9.9 points in the patient group [range 31–59], mean of 53.1 ± 4.8 in control group [range 41–60]. Patients also had lower scores in the Digit Span Backward Test (7.6 ± 2.4 [range 4–13] vs. 9.6 ± 1.8 points in the control group [range 7–13]) and the Memo-Test (8.4 ± 0.9 [range 6.0–9.6] vs. 9.0 ± 0.6 in the control group [range 7.0–9.5]). Performance did not differ significantly in the patient and healthy control group for all other tests (Digit Span, TAP, MWT, BDI). Performance on the PASAT with 1.2 s stimulus intervals (used for comparisons with brain volume) showed a tendency to correlate with performance on the Memo-Test (Spearman rank correlation coefficient [SRCC] = 0.41, $P = 0.08$) and the Digit Span Backward (SRCC = 0.41, $P = 0.08$). Results on the BDI did not correlate with scores on the PASAT (1.2 s interval, SRCC = −0.13, $P = 0.61$), Digit Span Backward (SRCC = 0.30, $P = 0.21$) or Memo-Test (SRCC = −0.32, $P = 0.18$). For subsequent comparisons of brain volume and cognitive status, we used the PASAT, because it constitutes the current reference task for the cognitive evaluation of MS-patients (Cutter et al., 1999); we chose the more difficult version of the test with 1.2 s interstimulus intervals, because the range of performance among patients and mean group difference in scores were greater than for the easier version with 2.4 s intervals.

Group differences in global GM and WM volumes

Patients showed a tendency towards a lower GM volume than healthy controls ($P = 0.10$, median estimate of GM volume in patient group, based on GM probability map, was 6.99×10^5 [range 6.13×10^5–7.91×10^5], median GM volume of healthy controls 7.13×10^5 [range 6.31×10^5–7.70×10^5]). When the group of patients was divided into patients with low performance (defined as a score lower than one standard deviation below the mean score of the control group, i.e., <34 points, $n = 10$) and patients with higher scores ($n = 9$), low performers had a reduced GM-volume compared to matched controls ($P < 0.05$, median estimate of GM volume in patient group 6.68×10^5 [range 6.13×10^5–7.04×10^5], median of matched control subjects 7.04×10^5 [range 6.31×10^5–7.42×10^5]), whereas patients with normal performance ($n = 9$) and their matched control subjects did not differ with regard to GM-volume ($P = 0.67$, median in patient group 7.16×10^5 [range 6.28×10^5–7.91×10^5], median in matched control subjects 7.13×10^5 [range 6.64×10^5–7.70×10^5]). There was no difference in WM volume ($P = 0.68$, median in patient group 4.33×10^5 [range 3.94×10^5–4.97×10^5], in control group 4.46×10^5 [range 3.83×10^5–5.21×10^5]) or global brain volume ($P = 0.45$, median in patient group 1.13×10^6 [range 1.02×10^6–1.27×10^6], median in control group 1.14×10^6 [range 1.02×10^6–1.26×10^6]) between patients and controls.

Table 2
Correlations between neuropsychological test performance and MRI measures of disease severity in group of MS-patients ($n = 19$)[a]

Tests	MRI measures					
	GM volume		WM volume		WM lesion volume	
	SRCC[b]	P	SRCC[b]	P	SRCC[b]	P
PASAT	0.54	0.02	0.11	0.67	0.25	0.31
Digit Span Backward	0.43	0.07	0.10	0.69	0.12	0.62
Memo-Test	0.30	0.22	−0.33	0.17	0.36	0.13

[a] Not corrected for multiple comparisons.
[b] Spearman rank correlation coefficient.

Table 3
Group comparisons of regional brain volume

Location	Brodmann area	MNI coordinates			*Z* value	*P* cluster-level corrected
		x	*y*	*z*		
Comparison of all 19 patients with 19 matched healthy control subjects[a]						
Less GM volume in 19 patients than in 19 matched healthy control subjects						
Left inferior frontal gyrus	44	−49	13	15	3.80	0.05
Left superior temporal cortex	38	−47	15	−11	4.90	0.05
Comparison of 10 patients with low PASAT performance with 10 matched healthy control subjects[a]						
Less GM volume in 10 patients than in 10 matched healthy control subjects						
Right superior frontal gyrus	10	26	67	−6	4.00	0.0001
Left anterior mid-frontal gyrus	9	−36	28	29	4.66	0.0001
Left inferior frontal gyrus	47	−39	14	−7	3.78	0.0001
Right inferior frontal gyrus	47	43	30	−9	4.25	0.001
Left insula		−51	18	−7	4.98	0.0001
Left inferior parietal cortex	39	−45	−53	23	3.78	0.02
Right inferior parietal cortex	40	60	−28	35	3.58	0.01
Left superior temporal gyrus	22	−53	6	−11	4.04	0.0001
Right superior temporal gyrus	22	68	−32	12	3.30	0.01
Left middle temporal gyrus	21	−62	−6	−13	4.25	0.0001
Right middle temporal gyrus	21	56	−14	3	3.43	0.01

[a] There were no areas that showed increased GM volume in patients compared to control subjects or regional group differences in WM volume.

Correlations of brain volume and lesion volume with clinical status and performance on neuropsychological test battery

In the patient group, but not in the control group, GM volume correlated with performance on the PASAT (SRCC = 0.54, P = 0.02). Results on the Digit Span Backward test and the Memo test did not correlate with global GM-volume (Table 2). In the control group, GM volume did not correlate with cognitive performance. WM volume and WM lesion volume failed to correlate with performance on neuropsychological tests in either group.

EDSS correlated with WM lesion volume (SRCC = 0.45, P = 0.05), but not with GM volume (SRCC = −0.14, P = 0.57) or WM volume (SRCC = −0.28, P = 0.24). Moreover, EDSS did not correlate with performance on the PASAT (SRCC = −0.22, P = 0.36), Digit Span Backward (SRCC = −0.36, P = 0.14) or Memo Test (SRCC = −0.32, P = 0.18). WM lesion volume correlated inversely with WM volume (SRCC = −0.70, P = 0.001), but not with GM volume (SRCC = −0.05, P = 0.84). Duration of disease did not correlate significantly with GM volume, WM volume or WM lesion volume.

Group differences in distribution of GM and WM

The patient group overall showed reduced cortical volume in a region located in left temporal and prefrontal cortex compared to the control group (Table 3, Fig. 1). In contrast, there were no regions with increased volume in the group of patients compared to the control group. WM volume did not differ between the groups. When the 10 patients with low performance on the PASAT were compared with matched control subjects, differences in GM volume were more pronounced than in the overall group comparison: Patients exhibited reduced GM volume in right superior frontal gyrus, left anterior mid-frontal gyrus, bilateral inferior frontal cortex and left insula as well as bilateral inferior

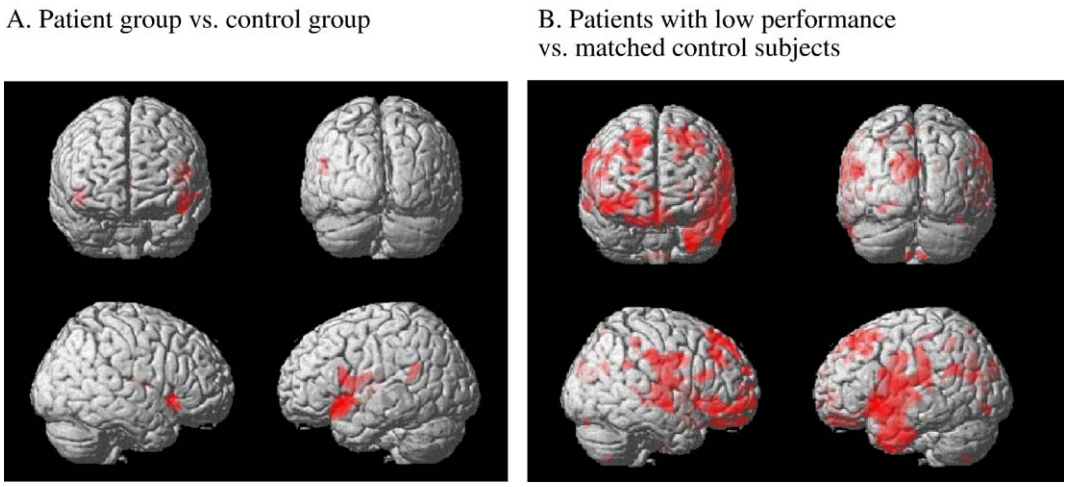

Fig. 1. Differences in regional GM volume between MS-patients and healthy control subjects. Note that the patient group overall showed decreased cortical volume in a region in left temporal and frontal cortex compared to healthy control subjects (A). Patients with low cognitive performance exhibited more extensive reductions in GM volume in bilateral frontal, temporal and parietal cortex (B), presented at $P < 0.005$.

Table 4
Correlations between regional GM volume and performance on PASAT

Location	Brodmann area	MNI coordinates			Z value	P cluster-level corrected
		x	y	z		
Correlations between regional GM volume and PASAT performance in patient group[a]						
Left superior frontal gyrus	10	−15	61	30	4.37	0.0001
Right superior frontal gyrus/ frontopolar cortex	10	23	67	14	4.34	0.0001
Right superior frontal gyrus	8	13	63	27	4.13	0.0001
Left anterior mid-frontal gyrus	46	−48	49	5	4.08	0.0001
Left posterior mid-frontal gyrus	9	−25	32	37	3.79	0.0001
Right posterior mid-frontal gyrus	46	47	34	19	4.44	0.0001
Left inferior frontal gyrus	45	−49	35	12	3.63	0.0001
Left precentral gyrus	6	−33	15	58	4.38	0.0001
Right precentral gyrus	6	49	14	48	4.00	0.0001
Left superior parietal lobe	7	−22	−53	70	3.88	0.0001
Right superior parietal lobe	7	25	−56	57	3.45	[§]
Left precuneus (superior parietal cortex)	7	−15	−49	75	3.62	0.05
Right cerebellum		25	−92	−34	4.10	0.05

[§] $P < 0.05$ voxel-level corrected after ROI analysis.
[a] There were no correlations between GM volume and cognitive performance in the control group or between WM volume and cognitive performance in either group.

parietal lobule (IPL) and superior and middle temporal cortex (Table 3, Fig. 1). Conversely, patients with normal performance did not show regional increases in GM volume compared to control subjects. There were no differences in regional WM volume between the two groups overall or between patients with low performance ($n = 10$) and their matched control subjects.

Correlations between regional distribution of GM and WM volume and performance on the PASAT

When PASAT performance was correlated with the distribution of GM volume, patients with lower performance exhibited reduced cortical volume in bilateral superior frontal gyrus (SFG), extending into frontopolar cortex in the right hemisphere, left anterior mid-frontal gyrus (MFG) and inferior frontal gyrus, bilateral posterior MFG, bilateral precentral gyrus, bilateral superior parietal cortex including left precuneus and right cerebellum (Table 4, Fig. 2).

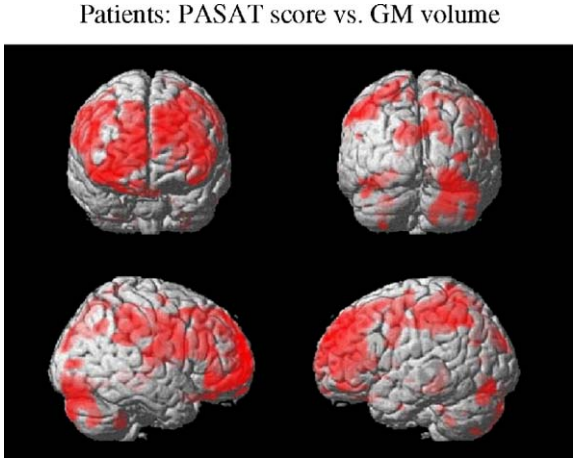

Fig. 2. Correlations between cognitive performance and regional GM volume in group of patients. Note that low performance was associated with reduced cortical volume in bilateral prefrontal, precentral, superior parietal and right cerebellar cortex, presented at $P < 0.005$.

Patients did not show inverse correlations between GM volume and performance on the PASAT. In the group of healthy control subjects, there were no significant correlations between cortical volume and PASAT score. Neither group showed correlations between WM volume and PASAT performance.

Discussion

The main findings of this study were a) that impaired cognitive performance in MS-patients correlated with reduced GM volume in cortical regions pertinent to task requirements and b) that patients with low cognitive performance showed more extensive cortical volume loss than matched control subjects in frontal, temporal and parietal regions, previously identified as foci of diffuse GM atrophy in MS (Sailer et al., 2003). The combination of these results points to a close association between cognitive impairment and cortical atrophy in patients with relapsing–remitting MS.

Group comparisons of GM and WM volume

Cortical thinning occurs early in MS and appears to be most pronounced in temporal and frontal cortex (Sailer et al., 2003). In the group comparison with matched control subjects, patients with low performance on the PASAT exhibited widespread reductions in cortical volume predominantly in these areas, while GM atrophy in the patient group overall was limited to one region located in left temporal and frontal cortex. The fact that GM atrophy among patients was mainly attributable to individuals with poor test scores, suggests that cognitive decline in these patients reflects the typical progression of MS-related cortical volume loss. The reasons for this pattern of atrophy are unclear. One possible explanation is that WM lesions tend to accumulate in periventricular areas (Brownell and Hughes, 1962; Narayanan et al., 1997) with fiber connections to specific cortical regions and may cause retrograde axonal damage of cortical neurons (Matthews et al., 1996; Sailer et al., 2003; Simon et al., 2000; Trapp et al., 1998). Contrary to some studies (Ge et al., 2000; Quarantelli et al., 2003), we did not detect a correlation between GM volume loss

and WM lesion load and thus found no evidence for Wallerian degeneration as a significant contributor to cortical atrophy. The limited number of patients studied as well as the fact that patients were analyzed at early stages of the disease may have contributed to the absence of significant correlations between GM atrophy and WM lesion load as well as EDSS. Cortical atrophy is likely to cause physical disability, especially when it progresses to the motor cortex in more advanced MS (Sailer et al., 2003). Conversely, widespread WM damage carries a high risk of cognitive impairment (Arnett et al., 1994; Rao et al., 1989; Swirsky-Sacchetti et al., 1992).

Another possible mechanism of cortical atrophy is primary GM pathology, which may consist of focal lesions, often not visible on conventional MRI (Bo et al., 2003; Kidd et al., 1999; Peterson et al., 2001), or might reflect a neurodegenerative component of the disease independent of focal lesions (Garbern et al., 2002). An emphasis of atrophy in specific cortical regions may, for example, result from an increased vulnerability to oxidative stress from inflammatory mediators (Wegner and Matthews, 2003).

In the current group of clinically early patients, global GM volume showed a tendency towards volume reduction compared with healthy subjects. The difference in GM volume was significant when patients with low cognitive performance were compared with matched controls, in line with a recent study that demonstrated global GM atrophy in patients with cognitive deficits (Amato et al., 2004). In contrast, WM volume including lesion volume did not differ between patients and healthy subjects, in accord with a previous analysis of relapsing–remitting patients (Quarantelli et al., 2003) and failed to show a correlation with cognitive performance.

Correlation between regional GM atrophy and cognitive performance

In the patient group, regional GM volume correlated with PASAT performance in bilateral prefrontal cortex, precentral gyrus and superior parietal lobe as well as left precuneus and right cerebellum.

Significantly, these cortical areas correspond to neuronal circuitry presumably engaged by the task. The PASAT is a complex test of executive function, working memory, information processing speed and divided attention (Gronwall, 1977) and places high demands specifically on cortical regions involved in the manipulation of information as well as the allocation of attention. Prefrontal cortex, especially the anterior part of mid-frontal cortex, which showed bilateral reductions in volume associated with low cognitive performance, has been found to be responsible for rehearsal and monitoring as well as manipulation of information in working memory (e.g., Cohen et al., 1997; Courtney, 2004; Courtney et al., 1998; D'Esposito et al., 1999; Pessoa et al., 2002; Petrides, 1995; Sakai et al., 2002). In the right hemisphere, prefrontal areas of reduced volume extended to the frontopolar cortex, known to be important for the performance of highly complex tasks requiring planning and problem solving (Christoff et al., 2001; Koechlin et al., 1999; Ramnani and Owen, 2004). More posterior frontal involvement included bilateral precentral and posterior mid-frontal cortex (Brodmann areas [BA] 6 and 44). While left BA 44 and 6 are considered important for verbal storage and rehearsal of presented stimuli in working memory (e.g., Awh et al., 1996; Baddeley and Hitch, 1994; Paulesu et al., 1993), presumably required by the PASAT, right precentral involvement may reflect the importance of memorizing temporal order during task performance (Hayes et al., 2004; Marshuetz et al., 2000; Wager et al., 2004). Of note, the PASAT was performed at a high level of difficulty with intervals of only 1.2 s, placing high demands on executive functioning and temporal sequencing.

PASAT scores in the patient group also correlated inversely with regional GM volume in bilateral superior parietal lobe and left precuneus, areas associated with the allocation of attentional resources within working memory, including object-based shifts in attention (Le et al., 1998; Serences et al., 2004), which were continuously required during performance of the PASAT. Moreover, bilateral SPL and precuneus have been found to be active during the performance of simple calculation and arithmetic tasks (Dehaene et al., 1996; Rickard et al., 2000; Sammer et al., 2005; Zago et al., 2001). Finally, patients exhibited a strong correlation between right lateral cerebellar volume and PASAT performance. Activation in the right cerebellar hemisphere is known to occur during articulatory rehearsal of phonological information in working memory (Desmond et al., 1997). In stroke patients, cerebellar lesions, especially lesions located in the right hemisphere, have been associated with deficits in executive function, working memory and divided attention (Gottwald et al., 2004). Recently, altered cerebellar function during performance of a working memory task was identified in MS-patients, prompting the conclusion that cerebellar damage may contribute to the working memory impairment observed in MS (Li et al., 2004). Overall, it seems likely that the correlations between cognitive performance and regional GM volume highlighted areas affected by diffuse cortical atrophy (Sailer et al., 2003), though not necessarily identical with regions of accentuated volume loss.

In functional imaging studies, the paced auditory or visual serial addition task has been found to engage similar cortical networks, though MS-patients and healthy controls tend to exhibit differences in the distribution or extent of cortical activation (Audoin et al., 2003; Lazeron et al., 2003; Mainero et al., 2004). Altered cortical activation in MS-patients during the performance of cognitive tasks could, at least in part, be compensatory (Audoin et al., 2003; Mainero et al., 2004; Morgen et al., 2004; Rocca et al., 2002; Staffen et al., 2002; Wishart et al., 2004). A combination of voxel-based mapping of cortical atrophy and functional imaging could provide further insights into the relationship between changes in cortical structure and function in MS.

In conclusion, the present study suggests that GM atrophy is directly associated with cognitive impairment in patients with relapsing–remitting MS. Whether our findings can be confirmed in a larger study including patients in more advanced stages of disease and correlation analyses between GM volume and additional measures of cognitive status remains to be investigated. The fact that cognitive impairment did not correlate significantly with physical disability or WM lesion load in the current group of patients emphasizes the relevance of cortical atrophy in MS as a measure of disease severity. Even in the absence of physical disability or substantial WM lesion load, evidence of GM atrophy may point to the importance of optimizing treatment.

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