doi:10.1093/brain/awn229 *Brain* (2008), **131**, 3222–3231

Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain–cognition interaction

R. Luerding,[1] T. Weigand,[2] U. Bogdahn[1] and T. Schmidt-Wilcke[1]

[1]Department of Neurology, University of Regensburg, Regensburg and [2]Clinic for Rheumatology, Asklepios Kilinikum Bad Abbach, Bad Abbach, Germany

Correspondence to: Tobias Schmidt-Wilcke, MD, Department of Neurology, Universitätsklinik Regensburg, Universitätsstraße 84, D-93053 Regensburg, Germany
E-mail: tobias.schmidt-wilcke@medbo.de

Fibromyalgia (FM) is a disorder of unknown aetiology, characterized by chronic widespread pain, stiffness and sleep disturbances. In addition, patients frequently complain of memory and attention deficits. Accumulating evidence suggests that FM is associated with CNS dysfunction and with an altered brain morphology. However, few studies have specifically investigated neuropsychological issues in patients suffering from FM. We therefore sought to determine whether neuropsychological deficits found in FM patients may be correlated with changes in local brain morphology specifically in the frontal, temporal or cingulate cortices. Twenty FM patients underwent extensive testing for potential neuropsychological deficits, which demonstrated significantly reduced working memory and impaired non-verbal long-term memory (limited to free recall condition) in comparison with normative data from age- and education-matched control groups. Voxel-based morphometry (VBM) was used to evaluate for potential correlations between test results and local brain morphology. Performance on non-verbal working memory was positively correlated with grey matter values in the left dorsolateral prefrontal cortex, whereas performance on verbal working memory (digit backward) was positively correlated with grey matter values in the supplementary motor cortex. On the other hand, pain scores were negatively correlated with grey matter values in the medial frontal gyrus. White matter analyses revealed comparable correlations for verbal working memory and pain scores in the medial frontal and prefrontal cortex and in the anterior cingulate cortex. Our data suggest that, in addition to chronic pain, FM patients suffer from neurocognitive deficits that correlate with local brain morphology in the frontal lobe and anterior cingulate gyrus, which may be interpreted to indicate structural correlates of pain–cognition interaction.

Keywords: fibromyalgia; chronic pain; neuropsychology; voxel-based morphometry

Abbreviations: ACC = anterior cingulate cortex; CLBP = chronic low back pain; CTTH = chronic tension type headache; DLPFC = dorsolateral prefrontal cortex; FM = fibromyalgia; FWE = family-wise error; Medial FG = medial frontal gyrus; MFG = middle frontal gyrus; PFC = prefrontal cortex; ROI = region of interest; SES = Schmerzempfindungsskala (pain experience scale); SMA = supplementary motor cortex; SSRI = selective serotonin reuptake inhibitor; VBM = voxel-based morphometry

Received February 29, 2008. Revised July 28, 2008. Accepted August 29, 2008. Advance Access publication September 26, 2008

Introduction

Fibromyalgia (FM) is a disorder of unknown aetiology (Merskey and Bogduk, 1994), characterized by chronic widespread musculoskeletal pain, stiffness and multiple tender points. While pain is the defining characteristic of FM, the disorder is frequently associated with depression, fatigue and sleep disturbances (Wolfe *et al.*, 1995). In addition, patients often complain of memory and attention deficits. There are only a few studies that have specifically investigated neuropsychological issues in patients suffering

from FM, and results remain heterogeneous. Some have described significant cognitive deficits, mostly in working memory performance (Park *et al.*, 2001; Dick *et al.*, 2002; Leavitt and Katz, 2006), others have either failed to detect such differences (Walitt *et al.*, 2008) or found that differences between groups disappeared after correcting for fatigue, pain and depression (Suhr, 2003). For example, Park *et al.* (2001) reported memory and vocabulary deficits with intact processing speed in FM patients. In contrast, Suhr (2003) suggested that most of the neuropsychological deficits found in FM can be explained by depression and fatigue.

By some authors FM is considered a stress-related disorder due to its frequent onset and exacerbation of symptoms in the context of stressful life events (Clauw and Crofford, 2003; Mease *et al.*, 2005). However, the specific pathophysiology responsible for FM remains unknown, and it is a still matter of debate whether pain in FM patients is predominantly caused by peripheral or central mechanisms (Vierck, 2006). Brain imaging studies in FM patients point to alterations in regional cerebral blood flow (Mountz *et al.*, 1995), in cerebral processing of sensory and nociceptive stimuli (Gracely *et al.*, 2002; Cook *et al.*, 2004) and in dopamine response to tonic pain (Wood *et al.*, 2007). So far, there are two studies that have specifically investigated brain morphology in FM patients using voxel-based morphometry (VBM). In a study that evaluated 10 FM patients and 10 healthy controls, Kuchinad *et al.* (2007) found decreased grey matter volume in several brain regions, including the cingulate, insular and medial frontal cortices, as well as in the left parahippocampal gyrus. In contrast, Schmidt-Wilcke *et al.* (2007) found a decrease in grey matter in the right superior temporal gyrus and the left posterior thalamus, as well as an increase in grey matter in the left cerebellum and in the striatum bilaterally. Altered brain morphology has been described in various other clinical pain conditions, including chronic back pain (Apkarian *et al.*, 2004; Schmidt-Wilcke *et al.*, 2006; Buckalew *et al.*, 2008), chronic tension type headache (Schmidt-Wilcke *et al.*, 2005), migraine (Kim *et al.*, 2008; Schmidt-Wilcke *et al.*, 2008; Valfre *et al.*, 2008) and phantom limb pain (Draganski *et al.*, 2006). Different pain conditions appear to be associated with different patterns of altered brain morphology, and it remains unclear whether prolonged pain experience causes brain changes or whether an altered brain morphology predisposes to pain amplification and/or chronification. However, there are various anatomical sites that are described time and again that are involved in pain perception, pain modulation and stress, such as the insular cortex (Schmidt-Wilcke *et al.*, 2005; Kuchinad *et al.*, 2007; Kim *et al.*, 2008), the cingulate cortex (Schmidt-Wilcke *et al.*, 2005; Kuchinad *et al.*, 2007; Schmidt-Wilcke *et al.*, 2008), the orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC) (Apkarian *et al.*, 2004; Schmidt-Wilcke *et al.*, 2008). One important question that arises is whether the symptoms that chronic pain patients display other than pain, such as behavioural or cognitive deficits, might be associated with the morphological alterations described. The anterior cingulate cortex, for example, has been shown to play an essential role not only in pain perception and pain control, but also in selective attention, working memory and error awareness (Klein *et al.*, 2007). The prefrontal cortex is critically involved not only in pain modulation (Petrovic and Ingvar, 2002), but also in executive functioning (Rusch *et al.*, 2007), working memory and recognition (Turriziani *et al.*, 2008), especially in the free recall. Thus, changes in the frontal or cingulate cortex might be associated with impaired working memory performance or executive functioning. On the other hand, changes in the medial temporal lobe, as described by Kuchinad *et al.* in FM patients and by Schmidt-Wilcke *et al.* in patients with chronic tension type headache, could possibly go along with deficits in long-term memory storage and retrieval. Although brain imaging has permitted insights as to the neural substrates of pain and pain–cognition interaction (Petrovic and Ingvar, 2002; Seminowicz and Davis, 2007; Baliki *et al.*, 2008), the mechanism of chronic pain interference with cognition and its relation to other concomitant disorders, such as depression, anxiety and chronic fatigue, need to be further elucidated. VBM has evolved into an important tool to investigate potential correlations between brain morphology and cognitive performance that has been predominantly applied not only in psychiatric disorders such as schizophrenia (Rusch *et al.*, 2007), depression (Vasic *et al.*, 2008) and dementia (Chetelat *et al.*, 2003), but also in patients with Huntington's disease (Peinemann *et al.*, 2005; Wolf *et al.*, 2008) and high blood pressure (Gianaros *et al.*, 2006). To our knowledge, there are no investigations that have specifically attempted to link cognitive data to brain morphology in FM or in other chronic pain conditions. We therefore sought to elucidate neuropsychological deficits in FM, as previously reported, and to determine how levels of performance on neuropsychological subtests might correlate with local brain morphology, specifically in the frontal, temporal or cingulate cortex. Twenty FM patients were evaluated and underwent extensive testing for potential neuropsychological deficits.

Patients reported herein had been compared with healthy controls in a previous study (within a cohort analysis, investigating differences in brain morphology between groups). A conspicuous pattern of altered brain morphology in several regions, including the thalamus, the cerebellum and the striatum had been described. Results of this cohort analysis were reported by our group as noted above (Schmidt-Wilcke *et al.* (2007).

Methods

Subjects

Twenty patients with FM [19 females, 1 male, mean age 53.6 years (SD = 7.7)] were recruited from the clinic for rheumatology, Asklepios-Klinikum Bad Abbach. All patients had been examined by an experienced rheumatologist and fulfilled the diagnostic criteria for FM according to the guidelines put forth by the American College of Rheumatology (Wolfe *et al.*, 1990). Patients

were not asked to alter their medications prior to study. All participants were thoroughly informed and gave written consent. Procedures of the study were explained in detail prior to testing. The study had been approved of by the local ethics committee.

Clinical pain

The clinical pain experience of FM patients was assessed using the pain experience scale (Schmerzempfindungsskala, SES), a validated German adaptation of the McGill Pain Questionnaire (Melzack, 1975). The SES consists of 24 items (14 affective and 10 sensory) that are rated by patients on a four-point scale based on the degree to which a given descriptor fits their experience: 'not applicable' (1), 'somewhat' (2), 'well' (3) or 'exactly'(4). The mean duration of pain among FM patients was 173 months (SD = 86.5).

Depressive symptoms

The Beck Depression Inventory (BDI) is a 21-item self-report used to assess the severity of depressive symptoms, including cognitive, behavioural, affective and somatic domains. Each item contains four statements indicating the degree of severity of the symptom. The BDI score is the sum of all items and ranges from 0 to 63. Scores of 10–19, 20–25 and >25 indicate mild, moderate and severe depressive symptoms, respectively (Beck and Steer, 1984).

Neuropsychological assessment

Verbal and non-verbal cognition was measured using a short form of the German version of the revised Wechsler Adult Intelligence Scale (Tewes, 1994) with subtests assessing general knowledge, comprehension, similarities, block design matrices, digit symbol test and picture completion. Verbal long-term memory was measured with the California Verbal Learning Test (CVLT); non-verbal long-term memory was measured with the Rey Visual Design Learning Test (RVDLT). Verbal working-memory was measured with the digit span backward and non-verbal working-memory with the Corsi block span. Trail Making Tests (Parts A and B; TMT A and B) provide a measure of complex conceptual tracking, planning and flexibility. All tests have been described and characterized by Lezak (Lezak, 1995). For clinical assessment, raw scores were transformed into *z*-scores adjusting for age, sex and education, using population-based, normative data (means and standard deviations), provided by the respective test author. For a complete list of tests and test authors see supplementary data (Table A1). A *z*-score between −1 and 1 indicates that an individual's performance is within 1 SD of the average performance of normal (healthy), age- and education-matched controls (i.e. within normal range). For each test a mean *z*-score was calculated from individual *z*-scores, indicating group performance (Fig. 1). A *z*-score of <1 was chosen as cut-off value to indicate an impaired performance. This was done in accordance with several other studies that investigated subtle cognitive deficits in neurological (Ziemus *et al.*, 2007; Heo *et al.*, 2008) and psychiatric diseases (Schmidtke and Hermeneit, 2008). From a clinical perspective, comparison with normative data has the advantage of enabling comparison of individual patients to a large, standardized group of age- and education-matched controls. In addition, the adjusted data were analysed for effects of depression with a correlation between BDI and *z*-scores. Working memory and long-term memory scores were compared using a paired *t*-test for differences of means in order to check for intra-subjective differences between working memory and long-term memory. This method is well suited to assess neuropsychological measures in a selected clinical patient group and has been applied in studies performed at our institute before (Ziemus *et al.*, 2007).

MR imaging and analysis

Data acquisition

Magnetic resonance imaging was performed on a Siemens Sonata system operating at 1.5 t. For each subject, a T_1-weighted gradient echo MP-RAGE sequence (TR 1880 ms, TE 3.93 ms, flip angle 15°, matrix size 256 × 192) yielding 176 sagittal slices with a defined voxel size of 1 × 1 × 1.08 mm. Inspection of individual MR images revealed no gross morphological abnormalities.

VBM protocol

VBM is based on high-resolution structural 3D-MR images, which are transformed into a common stereotactic space. It is designed to identify significant regional differences between groups and/or correlations between independent variables and grey/white matter values in one or more groups by applying voxel-wise statistics in the context of Gaussian random fields (Ashburner and Friston, 2000). VBM has been cross-validated with region-of-interest (ROI) measurements and functional data in a number of studies (May *et al.*, 1999; Gitelman *et al.*, 2001).

Data pre-processing and analysis were performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) running under Matlab, 7th Jan (Mathworks, Sherborn, MA, USA). Pre-processing of the data involved spatial normalization, segmentation and spatial smoothing with a Gaussian kernel. To facilitate optimal segmentation, we estimated normalization parameters while removing non-brain voxels (skull, sinus) using an optimized protocol (Good *et al.*, 2001). The optimized parameters, estimated while normalizing extracted grey matter images to the customized grey matter template, were reapplied to the original whole-brain images. The images were then aligned with the stereotactic space as defined by the Montreal Neurological Institute (MNI; www.loni.ucla.edu/ICBM/ICBM_Databases.html) and then corrected for non-uniformities in signal intensity and partitioned into grey matter, white matter, cerebrospinal fluid and background using a modified mixture model cluster analysis. Subsequently, all grey matter images were smoothed by convolving them with an isotropic Gaussian kernel of 10 mm full-width at half maximum and all white matter images with a Gaussian kernel of 16 mm full-width at half maximum.

Statistical analysis

The SPM analysis is an implementation of the general linear model using the theory of Gaussian random fields. We performed regression analyses to identify brain regions that show a significant correlation between grey/white matter values and behavioural data. One multiple regression analysis was conducted for verbal and non-verbal working memory data (verbal: digit span backward; non-verbal: Corsi block span); a second multiple regression analysis was conducted for long-term memory data (verbal: CVLT; non-verbal: RVDLT). Statistical analysis used the 'covariate-only' model in SPM2. Cognitive scores were entered as independent covariates (predictors) with age and global volume entered as nuisance variables. In order to elucidate possible correlations between pain experience, cognitive performance and local brain morphology,

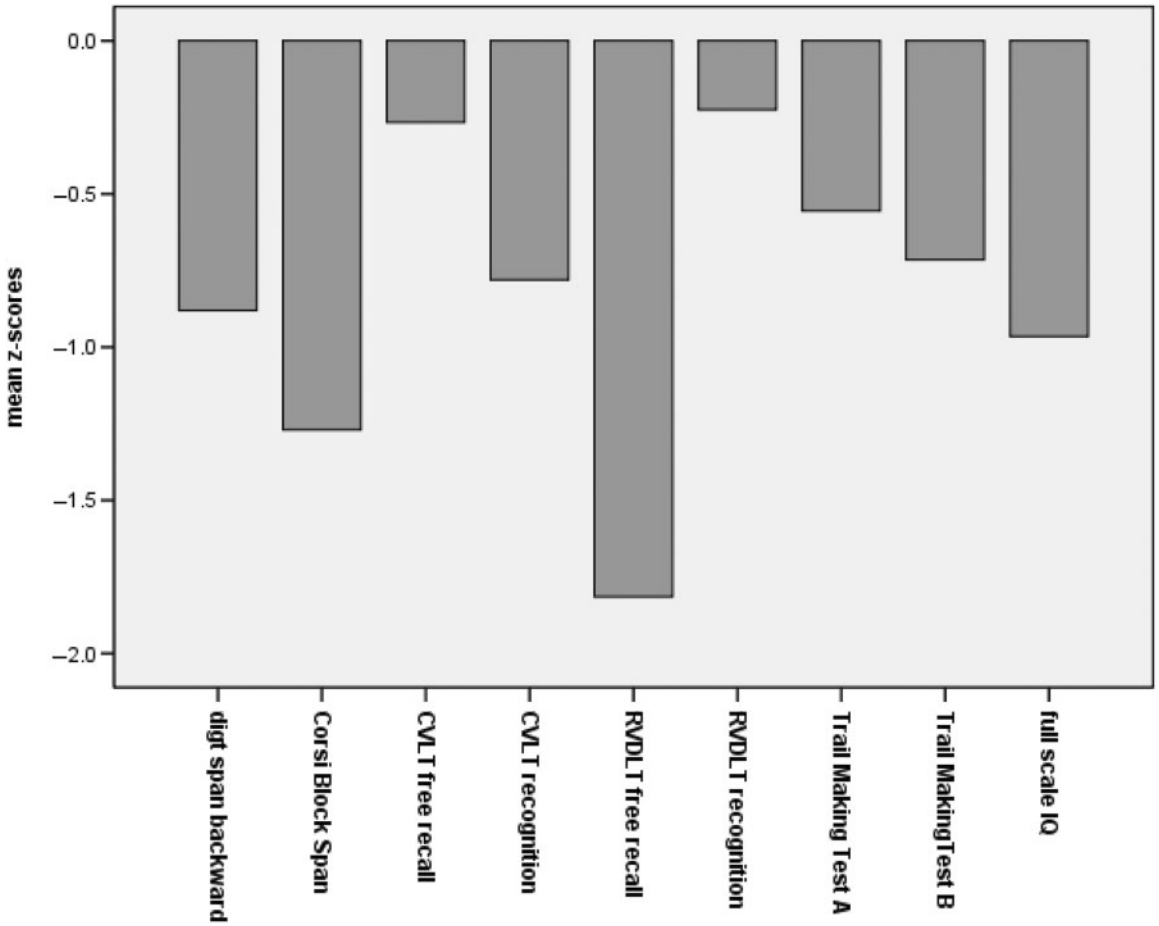

Fig. 1 Cognitive scores. Digit span backward (verbal working memory); Corsi block span (non-verbal working memory); CVLT (verbal long-term memory); RVDLT (non-verbal long-term memory); TMT A, TMT B (attention); full-scale IQ from revised Wechsler Adult Intelligence Scale.

we performed in a second step multiple regression analyses including working memory scores and pain scores (SES total, SES-A and SES-B). To avoid possible edge effects around the border between grey and white matter and to include only relatively homogenous voxels, we excluded all voxels with a matter value of <0.1 (of a maximum value of 1). In an analogous fashion, we performed white matter analyses, including age as a nuisance variable.

The correlation analysis tests the null hypothesis that the slope of a fitted regression (using least square solution) describing the relation between a predictor and an outcome variable is zero. A positive correlation means that grey matter values are highest in participants with high scores, while a negative correlation means that grey matter values are highest in participants with low scores. In a first step, we used a threshold of $P<0.001$ (uncorrected for multiple comparisons). Results were declared significant either on the cluster level ($P<0.05$ corrected) or on the peak level ($P<0.05$ corrected for multiple comparisons, family-wise error). For peak level analysis, our *a priori* hypotheses based on previously performed brain imaging studies and our behavioural data (pointing to a dysfunction of the frontal cortex) permitted the performance of ROI analyses for frontal brain areas (each frontal lobe) as a second step. Only results significant after correction for multiple comparisons will be reported.

Results

Neuropsychological assessment

Comparison to normative data

While FM patients showed a tendency towards reduced cognitive performance on most of the tests in comparison to normative data, only results from non-verbal working memory (block span, mean z-score = −1.27) and non-verbal long-term memory in the free recall condition (mean z-score = −1.81) were significantly reduced. Non-verbal long-term recognition (mean z-score = −0.23) was within normal range, indicating normal information storage but impaired retrieval.

Verbal working memory (digit span backward, mean z-score = −0.88), the verbal long-term memory free recall (mean z-score = −0.26) and recognition (mean z-score = −0.78) were within normal range in comparison with normative data, as were measures of attention (TMT B; mean z-score = −0.59), and full-scale IQ (mean z-score = −0.97). Data and results are summarized in Table 1 and Fig. 1.

Table 1 Results of the neuropsychological assessment, transformed into z-scores

Patient no.	BDI	SES	SES-A	SES-B	Corsi	Digit span backward	CVLT free recall	CVLT recognition	RVDLT free recall	RVDLT recognition	TMT B	TMT A	Full scale IQ
1	6	45	31	14	0.5	−0.9	0.90	−1.70	−0.90	−0.1	0.3	1.3	1.4
2	29	65	41	24	0.5	−2.5	−0.14	−1.70	−3.00	0.7	−3.0	−3.0	−2.7
3	16	79	48	31	−2.2	0.3	0.30	0.70	−0.10	−0.1	1.4	−0.2	1.1
4	13	51	32	19	−2.2	−1.0	−0.30	−0.50	−2.40	−0.8	−1.9	−1.3	−1.6
5	28	72	41	31	−2.2	−1.0	0.50	0.70	−0.70	0.7	1.2	0.1	−2.1
6	19	82	55	37	−1.4	−2.5	−1.50	−1.70	−2.00	−0.1	−0.1	−0.8	−1.9
7	27	45	31	14	−1.4	−0.2	1.20	0.70	−2.50	−0.1	−3.0	0.1	−0.8
8	5	57	31	26	−1.4	−0.9	−0.20	0.70	−1.90	0.7	−0.6	0.1	−1.3
9	7	39	21	18	−1.2	−1.0	1.20	0.70	−1.50	−0.1	1.8	1.5	−0.2
10	22	74	41	33	−2.2	−1.7	0.20	0.70	−1.00	−0.1	−0.5	−0.4	−0.7
11	13	58	33	25	−1.2	−0.3	−0.20	−3.00	1.00	−0.8	0	−1.0	−1.1
12	37	89	53	36	0.5	−1.7	−1.70	−1.70	−2.50	−0.1	−0.9	0.2	0.1
13	27	65	39	26	−1.2	−1.7	−1.40	−1.70	−2.40	−0.8	0	−0.8	−1.5
14	11	51	35	16	−1.4	−1.7	−0.50	−0.50	−3.00	−0.1	−1.6	0.6	−0.7
15	20	70	44	26	−2.4	−0.9	−0.18	−2.90	−3.00	−0.8	−2.6	−0.5	−2.3
16	12	68	39	29	0.5	−0.9	−2.90	−0.50	−2.20	0.7	−3.0	−2.2	−2.3
17	30	64	44	21	−1.2	1.0	0.80	0.70	−1.10	−0.1	−0.9	−1.6	0.4
18	20	60	40	20	−2.2	−0.3	−1.80	−2.90	−3.00	−1.6	−0.7	−0.5	−2.1
19	7	69	41	28	−1.4	0.6	−0.50	−1.20	−1.80	−0.8	−0.3	0	−0.5
20	13	67	41	36	−2.2	−0.3	0.90	−0.50	−2.30	−0.8	0.1	−2.7	−0.5

Comparison of working memory to long-term memory

In order to assess intra-individual differences between the performance on tests of long-term memory and working memory, *t*-tests for comparison of means were performed between measures of working memory and long-term memory. There was a significant difference between the mean *z*-score of digit span backward and the mean *z*-score of verbal long-term memory free recall (mean digit span backward = −0.88, mean CVLT free recall = −0.49, $T = -3.687$, df = 19, $P = 0.02$). However, there was no significant difference between the mean *z*-score of digit span backward and the mean *z*-score of verbal long-term memory recognition.

Mean *z*-scores of non-verbal working memory were significantly different from mean *z*-scores of non-verbal long-term memory recognition (Corsi block span = −1.27, RVDLT recognition = −0.23 $T = -5.156$, df = 19, $P < 0.001$). There was no significant difference between the mean *z*-score of non-verbal working memory and the mean *z*-score of non-verbal long-term memory free recall. Notably, performance on both verbal and non-verbal working memory evaluations was significantly lower than on those for long-term memory (Table A2).

BDI and SES scores, interference with neuropsychological performance

The CVLT free recall was negatively correlated with the SES total score ($r = -0.49$). Moreover, neither BDI scores nor pain scores (SES-A and SES-B scores) were significantly correlated with neuropsychological performance (*z*-scores and raw scores). BDI scores and SES-A (affective) scores, but not SES-B (sensory) scores, were positively correlated ($r = 0.55$; Table A3).

VBM

Grey matter analyses

Performance on the non-verbal working memory task (Corsi block span) was positively correlated with grey matter values in the left middle frontal gyrus (MFG; $x = -29$, $y = 50$, $z = -1$; *z*-score = 4.73; $r = 0.89$). Performance on the verbal memory task (digit span backward) was positively correlated with grey matter values in the right and left medial frontal cortex (superior frontal gyrus/supplementary motor area; $x = 5$, $y = 19$, z = 63; *z*-score = 4.06; $r = 0.82$). SES-B scores were negatively correlated with gray matter values in the right medial frontal gyrus ($x = 3$, $y = 36$, $z = 48$; *z*-score = 4,22; $r = -0.84$) and positively correlated with grey matter values in the left orbitofrontal cortex (OFC; $x = -15$, $y = 31$, $z = -12$; *z*-score = 5.27; $r = 0.92$). Conjunction analysis (grey matter, global null) for verbal working memory performance and SES-B scores revealed conjoint parametric maps in the right medial frontal gyrus ($x = 3$, $y = 16$, $z = 59$; *z*-score = 5.20), extending down to the anterior cingulate gyrus ($x = 3$, $y = 22$, $z = 40$; *z*-score = 3.93).

White matter analyses

White matter analyses revealed a positive correlation for verbal working memory scores (digit span backward) and white matter values in the mid-cingulum bilaterally ($x = 4$, $y = -9$, $z = 39$; *z*-score = 3.98; $r = 0.80$; $x = -8$, $y = 5$, $z = 39$;

Table 2 Areas of significant correlations between grey/white matter values and neuropsychological performance

Test	Region		Brodmann area	Talairach coordinates in mm (peak within a cluster)			Cluster size at $P < 0.001$	*z*-values	*r*-values (peak within a cluster)
				x	*y*	*z*	*k*		
1. Multiple regression, Corsi block span and Digit backward as predictors (age and global volume as nuisance variable)—grey matter analysis									
Corsi Block span	MFG	L	BA 10	−29	50	−1	451	4.73[a]	−0.89
Digit backward	SFG/SMA	R/L	BA 6	5	19	63	751	4.06[b]	−0.82
2. Multiple regression, Digit backward and SES-B as predictors (age and global volume as nuisance variable)—grey matter analysis									
Digit backward	SFG/SMA		BA 6	5	19	63	556	3.90	−0.81
SES-B	Medial FG	R	BA 8	3	36	48	1829	4.22[b]	−0.84
	OFC	L	BA 25/47	−15	31	−12	910	5.27[c]	−0.92
3. Multiple regression, Digit backward and SES-B as predictors (age as nuisance variable)—white matter analysis									
Digit backward	Midcingulum/ACC	R/L		−8	5	39	8309	4.18[b]	
				−13	20	34		4.15[b]	
				4	−9	39		3.98[b]	
SES-B	Perigenual ACC/OFC	L		−14	31	−13	4676	4.93[b]	−0.89
	ACC	R/L		−6	15	33	2119	4.11[b]	−0.81

Significant correlations between neuropsychological scores/pain scores and grey/white matter values are tabulated in terms of the brain region.
The corresponding Brodmann areas; the *x*, *y*, *z* coordinates are according to the atlas of Tailrach and Tournoux.
Each location is the peak within a cluster (defined as the voxel with the highest z-value).
L = left; R = right; Medial FG = medial frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus.
[a]Corrected for multiple comparisons (peak level, ROI analysis, left frontal lobe). [b]Corrected for multiple comparisons (cluster level).
[c]This result was already reported in Schmidt-Wilcke *et al*. (2007).

z-score = 4.18; $r = 0.82$) and the left anterior cingulate cortex (ACC; $x = -13$, $y = 20$, $z = 34$; *z*-score = 4.15; $r = 0.82$). Furthermore there was a negative correlation for SES-B scores and white matter values in the right mid-cingulum ($x = 6$, $y = -10$, $z = 40$; *z*-score = 4.05, $r = -0.80$) and the left ACC (rostral ACC: $x = -6$, $y = 15$, $z = 33$; *z*-score = 4.11, $r = -0.81$; and perigenual ACC/OFC: $x = -14$, $y = 31$, $z = -13$; *z*-score = 4.93, $r = -0.89$). Conjunction analysis (white matter, global null) revealed conjoint parametric maps in the right midcingulum ($x = 4$, $y = -9$, $z = 40$, *z*-score = 4.69), left ACC ($x = -9$, $y = 14$, $z = 34$; *z*-score = 4.78) and left medial frontal gyrus ($x = -19$, $y = -10$, $z = 53$; *z*-score = 4.02).

There were no regions demonstrating significant correlations (whether positive or negative) between grey matter values and long-term memory performance or executive function (TMT A or B). Performing statistical analyses with *z*-scores rather than raw scores (without age as nuisance variable) yielded comparable results. Brodmann areas, coordinates and *z*-scores are listed in Table 2, some of the corresponding parametric maps are shown in Fig. 2.

Discussion

This study investigated morphological correlates of cognitive performance in FM in an effort to extend previous investigations into morphological changes in pain patients by providing concomitant neuropsychological data.

Although cognitive complaints are a well-known phenomenon among FM patients, literature on neuropsychological investigations in FM is sparse, and results remain heterogeneous. Neuropsychological deficits in patients suffering from FM have been described in several studies before, mostly in working memory performance (Park *et al*., 2001; Dick *et al*., 2002; Leavitt and Katz, 2006), which seems to be especially susceptible to distraction (Leavitt and Katz, 2006; Glass *et al*., 2007). Others have either failed to detect significant differences in cognitive performance between FM patients and controls (Walitt *et al*., 2008) or found that differences between groups disappeared after correcting for fatigue, pain and depression (Suhr, 2003). In our evaluation, cognitive performance of FM patients was impaired in non-verbal working memory and non-verbal long-term memory in the free recall condition. Non-verbal recognition was within normal range, indicating normal information storage but reduced retrieval. Furthermore, FM patients displayed an impaired verbal working memory when compared to their verbal long-term memory performance. There were no significant correlations between BDI scores or SES scores and cognitive impairment, apart from a negative correlation between SES (total) scores and CVLT scores (free recall condition). Our data point to a dysfunction of the frontal cortex (rather than the temporal/hippocampal regions) which is critically involved in working memory and free recall of memory contents. This is in line with a recently performed study by Glass *et al*. (2007), who demonstrated that working memory impairment in FM patients is due to difficulties in managing competing/distracting information rather than

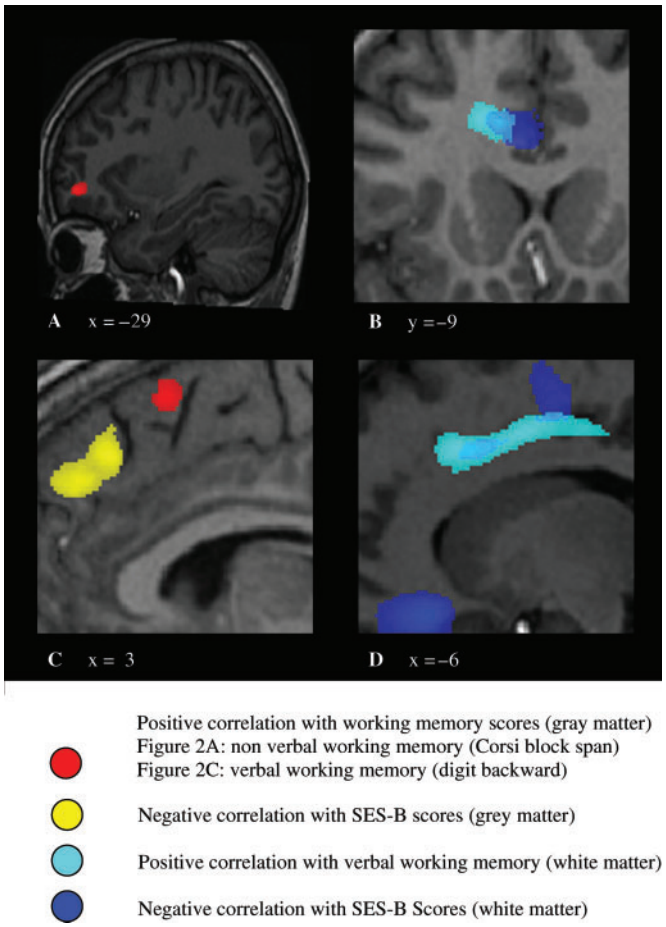

Fig. 2 Statistical parametric maps of regression analyses. (**A**–**D**) Statistical parametric maps demonstrating correlations between predictors and grey/white matter values (within the patients' group). Significant correlations are super-imposed in red (positive correlations working memory scores/grey matter values. (**A**) Non verbal working memory scores/grey matter values; (**C**) verbal working memory scores/grey matter values), in yellow (negative correlation SES-B scores/grey matter values), in turquoise [positive correlation verbal working memory scores/white matter values; (**B**) and (**D**)] and in blue [negative correlation SES-B scores/white matter values; (**B**) and (**D**)]. The left side of the picture is the left side of the brain (**B**). Voxels significant at $P < 0.001$.

to an accelerated loss of information. The reason why FM patients display, in addition to chronic pain, such cognitive deficits is unclear. Memory impairment and pain might either be concomitant, in terms of a co-occurrence, possibly sharing the same underlying pathophysiological process; alternatively, pain and cognition might share the same or at least communicating networks, whereby pain has an occupying and/or disabling effect on the working memory network (Seminowicz and Davis, 2007). Thus, one's having to cope with pain during the performance of a cognitive task might lead to a decreased availability of resources for cognitive performance (Park *et al.*, 2001).

We therefore sought to determine whether neuropsychological deficits or pain scores correlate with local brain morphology and whether potential correlations might be found in the same and/or neighbouring brain regions. Non-verbal working memory was positively correlated with grey matter values in the left middle frontal gyrus, whereas performance of the verbal working memory (digit span backward) was positively correlated with grey matter values in the supplementary motor area (SMA), respectively white matter values in the anterior cingulate cortex. No other test performance was significantly correlated with grey matter values in any brain region. SES B scores, on the other hand, correlated negatively with grey matter values in right medial frontal/prefrontal cortex and the cingulate cortex bilaterally.

Our results are in line with other studies investigating structural correlates of working memory performance. For example, Amici *et al.* (2007) describe verbal working memory deficits (digit span backward) in 58 patients with neurodegenerative diseases that were correlated with grey matter values in the right and in the left DLPFC, as well as in the left inferior parietal lobule. Gianaros *et al.* (2006) found a positive correlation between grey matter values and verbal working memory performance in the SMA, in the superior frontal gyrus and the anterior cingulate gyrus in male patients with high blood pressure. Functional imaging studies have previously revealed a network of cerebral structures activated during working memory performance. This functional network contains the DLPFC and the SMA, among other cortical and subcortical regions, (Jonides *et al.*, 1998; Cabeza and Nyberg, 2000; Ziemus *et al.*, 2007). In young adults, activation in the DLPFC is predominantly left lateralized for verbal working memory and right lateralized for non-verbal working memory. However, the degree of hemispherical lateralization is variable and seems to be age-dependent (Reuter-Lorenz *et al.*, 2000). In older adults, both verbal and non-verbal memory tasks tend to induce bilateral activation patterns in frontal regions; even paradoxical laterality is reported, possibly as an expression of compensation (i.e. functional plasticity) for neural decline. In our study, age is unlikely to be the driving force as it was added as a nuisance variable in all regression analyses. By means of interpretation, either the left MFG is critically involved in non-verbal working memory in FM and the cluster reported herein refers to a primary pathology, or it may be hypothesized that this finding indicates a cortical adaptation supporting cognitive performance, formerly based on right-sided processing, which then could be understood as a form of adaptive structural plasticity.

The medial frontal cortex, including the supplementary motor cortex (SMA, BA 6/8; adjacent to the ACC), seems to play an essential role not only in working memory but also in executive function, especially in the hierarchical organization of information processing (Rushworth *et al.*, 2004; Alexander *et al.*, 2007) and error awareness (Klein *et al.*, 2007). In our study, digit span backward scores and SES-B scores showed significant correlations with grey matter values in neighbouring brain regions (SMA and

medial frontal/prefrontal cortex, with partial overlap), whereas correlation analyses with white matter values revealed significant correlations in the corresponding subcortical areas, extending down to the cingulate cortex. Recent functional imaging studies have demonstrated a role for the SMA and medial frontal cortex in pain–cognition interaction, thereby suggesting that the processing of (experimental) pain and cognitive contents share similar neuronal networks, with a critical role indicated for the SMA, DLPFC and ACC in this interaction (Douaud *et al.*, 2006; Craggs *et al.*, 2007; Seminowicz and Davis, 2007). Interestingly, experimental pain was demonstrated to enhance functional connectivity within brain networks evoked by cognitive tasks (Seminowicz and Davis, 2007).

Little is known, however, regarding the impact of chronic (spontaneous) pain on this system. In an investigation of patients with chronic low back pain, Baliki *et al.* (2008) demonstrated that patients and healthy controls showed a similar activation pattern (including medial frontal cortex and ACC) when performing a visual spatial attention task, but patients exhibited significantly less deactivation than healthy subjects in the medial prefrontal cortex (including perigenual regions), which suggests an impairment (decreased deactivation) of the task negative (default mode) network. This network is involved in self-referential (emotional) processes and shows a deactivation when a cognitive task is being performed (Seminowicz and Davis, 2007; Baliki *et al.*, 2008). Thus, chronic pain, being associated with a hyperexcitability of the default network, possibly disables cognitive performance, which requires a deactivation of this system. In our study, the grey matter cluster that was correlated with SES-B scores lies at the frontal–prefrontal intersection, thus in the transition zone between the task-positive (including the SMA) and the task-negative (including the medial prefrontal cortex) network. Correlations for SES-B scores and verbal working memory with white matter values even showed a clear overlap in the medial frontal cortex and cingulate cortex. Thus, morphological changes associated with pain and deficits in working memory project to neighbouring and partially overlapping regions, which from a functional point of view possibly subserve opposing networks. However, for FM so far no imaging studies investigating pain–cognition interaction exist, and analogies should be regarded with caution.

VBM cannot disclose the neurobiological basis for morphological differences that are revealed. Assumptions regarding the underlying cytoarchitecture remain speculative for now. Variance in grey matter values could be caused not only by varying numbers of neurons, interneurons or glia cells, but also by differences in cell size. On a neurobiological level, it has been postulated that a decline, possibly caused by a persistent nociceptive input to the brain, could account for neural hyperexcitability on various levels of the central nervous system promoting the development of chronic pain (Moore *et al.*, 2002). Cognitive networks could either be influenced directly by such a persistent nociceptive input or indirectly, following changes in the (communicating) pain network. It is quite conceivable that such a decline (of inhibitory interneurons) would be detectable by VBM (Apkarian *et al.*, 2004).

In recent years, it has been postulated that a hypodopaminergic state might also contribute to the development and/or maintenance of chronic pain in FM patients (Wood, 2004; Holman and Myers, 2005; Wood *et al.*, 2007). Moreover, the impact of dopamine and dopamine deficiency in the prefrontal cortex on working memory performance has extensively been investigated (Apud *et al.*, 2007; Xu *et al.*, 2007). Following this line of thought, one could hypothesize that, in FM, a chronic lack of local dopamine (caused, for example, by a disruption of mesocortical projections to the medial frontal and prefrontal cortex) has an impact on local brain morphology and promotes cerebral vulnerability to the development of pain and working memory impairment.

Some limitations of this study need to be addressed. Metabolic and pharmacological issues, such as the amount and/or type of pain medication might play a role in both cognitive performance and brain morphology. As stated, there was no washout period prior to scanning. However, no medications that have been noted specifically to influence working memory, such as dopaminergic or antipsychotic drugs, were being taken by our subjects. While some of subjects were taking non-steroidal anti-inflammatory drugs, there are no data to suggest that these have a significant impact on cognition (Kang *et al.*, 2007; Grodstein *et al.*, 2008). Function of the frontal lobe, such as free recall of memory contents, is for example influenced by ketamine. However, none of our subjects were taking ketamine or related compounds. Temporal lobe functioning, on the other hand, is affected by benzodiazepines and opioids (Ghoneim, 2004), these effects are measurable particularly after application of a single dosage or in the period of augmentation. However, when taken chronically, which allows for the establishment of a steady state, the reported effects on recognition are no longer detectable (Friswell *et al.*, 2008). From this point of view, it is unlikely that pain medication had a major impact on cognitive performance in our study. As to brain morphology, there is evidence that antidepressants (SSRI) lead to an increase in hippocampal volume (Bremner, 2006) and protect against stress-induced insults to neuronal function and integrity. Furthermore, opioids have an impact on neuronal branching and spine density (Robinson and Kolb, 2004). In our study, only two patients took SSRIs and four patients took opioids at the time of scanning. Generally, we cannot rule out the possibility that the differences in medication intake and/or metabolic issues might account for some of the reported variance. This problem is not easy to resolve. Besides obvious ethical concerns, there are not criteria established to determine the length of a washout period in order to reverse potential behavioural and structural alterations that

might be caused by medication intake. Limitations of VBM concerning the underlying neurobiology have already been addressed, and functional interpretation of morphological results remains speculative. Thus, the question whether pain and cognitive impairment share an underlying pathophysiological process or if cognitive impairment is primarily caused by a pain-induced network overload cannot be answered. Finally, it remains unclear whether the changes found are associated with chronic pain or whether they are specific to FM.

In summary, our results extend the findings of other studies that have reported patients suffering from FM display neuropsychological impairments. In addition, we show that the degree of some of these impairments correlates with local brain morphology in the frontal lobe and the cingulate cortex. This is a first attempt to map neuropsychological deficits in FM patients to a specific brain region and to show that changes associated with such deficits and those associated with pain project to neighbouring, partially overlapping regions. Changes might either refer to a primary pathology or reveal a morphological adaptation in terms of a compensatory mechanism. Although our data demonstrate once more that pain and concomitant symptoms in FM are associated with alterations in the CNS, it cannot be concluded from these findings that FM is primarily a CNS disorder, since the alterations found could also represent a consequence of prolonged nociceptive input. Future longitudinal studies investigating the onset and course of FM are required to elucidate the interaction between brain plasticity, chronic pain and cognitive impairment. The notion that at least a subset of FM patients suffer from objective cognitive deficits has clinical implications, because it suggests that FM patients may benefit from sensitive neuropsychological evaluation, and that targeted treatment could result in an amelioration of these symptoms.

Supplementary material

Supplementary material is available at BRAIN online.

Acknowledgement

The authors wish to thank all volunteers for participation in this study and also P.B. Wood, M. Greenlee and S. Schwab-Malek for valuable discussions.

Funding

University of Regensburg grant (Reform B to T. Schmidt-Wilcke).

References

Alexander MP, Stuss DT, Picton T, Shallice T, Gillingham S. Regional frontal injuries cause distinct impairments in cognitive control. Neurology 2007; 68: 1515–23.

Amici S, Brambati SM, Wilkins DP, Ogar J, Dronkers NL, Miller BL, et al. Anatomical correlates of sentence comprehension and verbal working memory in neurodegenerative disease. J Neurosci 2007; 27: 6282–90.

Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 2004; 24: 10410–5.

Apud JA, Mattay V, Chen J, Kolachana BS, Callicott JH, Rasetti R, et al. Tolcapone improves cognition and cortical information processing in normal human subjects. Neuropsychopharmacology 2007; 32: 1011–20.

Ashburner J, Friston KJ. Voxel-based morphometry–the methods. Neuroimage 2000; 11: 805–21.

Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci 2008; 28: 1398–403.

Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol 1984; 40: 1365–7.

Bremner JD. The relationship between cognitive and brain changes in posttraumatic stress disorder. Ann NY Acad Sci 2006; 1071: 80–6.

Buckalew N, Haut MW, Morrow L, Weiner D. Chronic pain is associated with brain volume loss in older adults: preliminary evidence. Pain Med 2008; 9: 240–8.

Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 2000; 12: 1–47.

Chetelat G, Desgranges B, de la Sayette V, Viader F, Berkouk K, Landeau B, et al. Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. Brain 2003; 126: 1955–67.

Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003; 17: 685–701.

Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol 2004; 31: 364–78.

Craggs JG, Price DD, Verne GN, Perlstein WM, Robinson MM. Functional brain interactions that serve cognitive-affective processing during pain and placebo analgesia. Neuroimage 2007; 38: 720–9.

Dick B, Eccleston C, Crombez G. Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. Arthritis Rheum 2002; 47: 639–44.

Douaud G, Gaura V, Ribeiro MJ, Lethimonnier F, Maroy R, Verny C, et al. Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study. Neuroimage 2006; 32: 1562–75.

Draganski B, Moser T, Lummel N, Ganssbauer S, Bogdahn U, Haas F, et al. Decrease of thalamic gray matter following limb amputation. Neuroimage 2006; 31: 951–7.

Friswell J, Phillips C, Holding J, Morgan CJ, Brandner B, Curran HV. Acute effects of opioids on memory functions of healthy men and women. Psychopharmacology (Berl) 2008; 198: 243–50.

Ghoneim MM. Drugs and human memory (part 2). Clinical, theoretical, and methodologic issues. Anesthesiology 2004; 100: 1277–97.

Gianaros PJ, Greer PJ, Ryan CM, Jennings JR. Higher blood pressure predicts lower regional grey matter volume: consequences on short-term information processing. Neuroimage 2006; 31: 754–65.

Gitelman DR, Ashburner J, Friston KJ, Tyler LK, Price CJ. Voxel-based morphometry of herpes simplex encephalitis. Neuroimage 2001; 13: 623–31.

Glass JM, Park DC, Crofford LJ, Fougnie D, Clauw DJ. Working Memory in Fibromyalgia Patients: Impaired Function Caused by Distracting Information, Not Rapid Decay of Stored Information. ACR 2007 (abstract) 2007; Presentation number 115.

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 2001; 14: 21–36.

Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002; 46: 1333–43.

Grodstein F, Skarupski KA, Bienias JL, Wilson RS, Bennett DA, Evans DA. Anti-inflammatory agents and cognitive decline in a bi-racial population. Neuroepidemiology 2008; 30: 45–50.

Heo JH, Lee KM, Paek SH, Kim MJ, Lee JY, Kim JY, et al. The effects of bilateral Subthalamic Nucleus Deep Brain Stimulation (STN DBS) on cognition in Parkinson disease. J Neurol Sci 2008; 19–24.

Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum 2005; 52: 2495–505.

Jonides J, Schumacher EH, Smith EE, Koeppe RA, Awh E, Reuter-Lorenz PA, et al. The role of parietal cortex in verbal working memory. J Neurosci 1998; 18: 5026–34.

Kang JH, Cook N, Manson J, Buring JE, Grodstein F. Low dose aspirin and cognitive function in the women's health study cognitive cohort. Br Med J 2007; 334: 987.

Kim JH, Suh SI, Seol HY, Oh K, Seo WK, Yu SW, et al. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. Cephalalgia 2008; 28: 598–604.

Klein TA, Endrass T, Kathmann N, Neumann J, von Cramon DY, Ullsperger M. Neural correlates of error awareness. Neuroimage 2007; 34: 1774–81.

Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? J Neurosci 2007; 27: 4004–7.

Leavitt F, Katz RS. Distraction as a key determinant of impaired memory in patients with fibromyalgia. J Rheumatol 2006; 33: 127–32.

Lezak MD. Neuropsychological assessment. New York: Oxford University Press; 1995. p. 333–735.

May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 1999; 5: 836–8.

Mease PJ, Clauw DJ, Arnold LM, Goldenberg DL, Witter J, Williams DA, et al. Fibromyalgia syndrome. J Rheumatol 2005; 32: 2270–7.

Melzack R. The McGill Questionnaire: major properties and scoring methods. Pain 1975; 1: 277–99.

Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Monograph for the Task Force of taxonomy. 2nd edn. Seattle, WA: International Association for the Study of Pain; 1994: 45–7.

Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. J Neurosci 2002; 22: 6724–31.

Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, et al. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Arthritis Rheum 1995; 38: 926–38.

Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. Arthritis Rheum 2001; 44: 2125–33.

Peinemann A, Schuller S, Pohl C, Jahn T, Weindl A, Kassubek J. Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study. J Neurol Sci 2005; 239: 11–9.

Petrovic P, Ingvar M. Imaging cognitive modulation of pain processing. Pain 2002; 95: 1–5.

Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, et al. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 2000; 12: 174–87.

Robinson TE, Kolb B. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 2004; 47 (Suppl 1): 33–46.

Rusch N, Spoletini I, Wilke M, Bria P, Di Paola M, Di Iulio F, et al. Prefrontal-thalamic-cerebellar gray matter networks and executive functioning in schizophrenia. Schizophr Res 2007; 93: 79–89.

Rushworth MF, Walton ME, Kennerley SW, Bannerman DM. Action sets and decisions in the medial frontal cortex. Trends Cogn Sci 2004; 8: 410–7.

Schmidt-Wilcke T, Ganssbauer S, Neuner T, Bogdahn U, May A. Subtle grey matter changes between migraine patients and healthy controls. Cephalalgia 2008; 28: 1–4.

Schmidt-Wilcke T, Leinisch E, Ganssbauer S, Draganski B, Bogdahn U, Altmeppen J, et al. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. Pain 2006; 125: 89–97.

Schmidt-Wilcke T, Leinisch E, Straube A, Kampfe N, Draganski B, Diener HC, et al. Gray matter decrease in patients with chronic tension type headache. Neurology 2005; 65: 1483–6.

Schmidt-Wilcke T, Luerding R, Weigand T, Jurgens T, Schuierer G, Leinisch E, et al. Striatal grey matter increase in patients suffering from fibromyalgia–a voxel-based morphometry study. Pain 2007; 132 (Suppl 1): S109–16.

Schmidtke K, Hermeneit S. High rate of conversion to Alzheimer's disease in a cohort of amnestic MCI patients. Int Psychogeriatr 2008; 20: 96–108.

Seminowicz DA, Davis KD. Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task. J Neurophysiol 2007; 97: 3651–9.

Suhr JA. Neuropsychological impairment in fibromyalgia: relation to depression, fatigue, and pain. J Psychosom Res 2003; 55: 321–9.

Tewes U. Handbuch und Testanweisungen für den Hamburg-Wechsler Intelligenztest für Erwachesene Revision 1991. Hans Huber, Bern, Göttingen, Toronto, Seattle; 1994.

Turriziani P, Oliveri M, Salerno S, Costanzo F, Koch G, Caltagirone C, et al. Recognition memory and prefrontal cortex: dissociating recollection and familiarity processes using rTMS. Behav Neurol 2008; 19: 23–7.

Valfre W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. Headache 2008; 48: 109–17.

Vasic N, Walter H, Hose A, Wolf RC. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. J Affect Disord 2008; 109: 107–16.

Vierck CJ Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). Pain 2006; 124: 242–63.

Walitt B, Roebuck-Spencer T, Bleiberg J, Foster G, Weinstein A. Automated neuropsychiatric measurements of information processing in fibromyalgia. Rheumatol Int 2008; 28: 561–6.

Wolf RC, Vasic N, Schonfeldt-Lecuona C, Ecker D, Landwehrmeyer GB. Cortical dysfunction in patients with Huntington's disease during working memory performance. Hum Brain Mapp 2008; [Epub ahead of print].

Wolfe F, Ross K, Anderson J, Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. J Rheumatol 1995; 22: 151–6.

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990; 33: 160–72.

Wood P. Stress and dopamine: implication for the pathophysiology of chronic widespread pain. Medical Hypotheses 2004; 62: 420–4.

Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, et al. Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci 2007; 25: 3576–82.

Xu H, Kellendonk CB, Simpson EH, Keilp JG, Bruder GE, Polan HJ, et al. DRD2 C957T polymorphism interacts with the COMT Val158Met polymorphism in human working memory ability. Schizophr Res 2007; 90: 104–7.

Ziemus B, Baumann O, Luerding R, Schlosser R, Schuierer G, Bogdahn U, et al. Impaired working-memory after cerebellar infarcts paralleled by changes in BOLD signal of a cortico-cerebellar circuit. Neuropsychologia 2007; 45: 2016–24.