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Neural correlates of the chronic fatigue syndrome—an fMRI study

Floris P. de Lange,¹ Joke S. Kalkman,² Gijs Bleijenberg,² Peter Hagoort,¹ Sieberen P. vd Werf,³ Jos W. M. van der Meer⁴ and Ivan Toni¹

¹F.C. Donders Centre for Cognitive Neuroimaging, University of Nijmegen and ²Expert Centre for Chronic Fatigue, ³Department of Medical Psychology and ⁴Department of Internal Medicine, University Medical Centre, Nijmegen, The Netherlands

Correspondence to: Floris de Lange, F.C. Donders Centre for Cognitive Neuroimaging, University of Nijmegen, NL-6500 HB Nijmegen, The Netherlands
E-mail: floris.delange@fcdonders.kun.nl

Summary

Chronic fatigue syndrome (CFS) is characterized by a debilitating fatigue of unknown aetiology. Patients who suffer from CFS report a variety of physical complaints as well as neuropsychological complaints. Therefore, it is conceivable that the CNS plays a role in the pathophysiology of CFS. The purpose of this study was to investigate neural correlates of CFS, and specifically whether there exists a linkage between disturbances in the motor system and CFS. We measured behavioural performance and cerebral activity using rapid event-related functional MRI in 16 CFS patients and 16 matched healthy controls while they were engaged in a motor imagery task and a control visual imagery task. CFS patients were considerably slower on performance of both tasks, but the increase in reaction time with increasing task load was similar

between the groups. Both groups used largely overlapping neural resources. However, during the motor imagery task, CFS patients evoked stronger responses in visually related structures. Furthermore, there was a marked between-groups difference during erroneous performance. In both groups, dorsal anterior cingulate cortex was specifically activated during error trials. Conversely, ventral anterior cingulate cortex was active when healthy controls made an error, but remained inactive when CFS patients made an error. Our results support the notion that CFS may be associated with dysfunctional motor planning. Furthermore, the between-groups differences observed during erroneous performance point to motivational disturbances as a crucial component of CFS.

Keywords: chronic fatigue syndrome; motor planning; fMRI; anterior cingulate; motivation

Abbreviations: ACC = anterior cingulate cortex; BDI = Beck depression inventory; BOLD = blood oxygenation level-dependent; CFS = chronic fatigue syndrome; ER = error rate; fMRI = functional MRI; ITI = intertrial interval; HC = healthy controls; MI = motor imagery; RT = reaction time; VI = visual imagery

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Introduction

Chronic fatigue syndrome (CFS) is defined by persistent or relapsing unexplained fatigue, of new or definite onset and lasting for at least 6 months (Fukuda *et al.*, 1994). Patients who suffer from CFS report a variety of physical complaints such as headaches, unrefreshing sleep and post-exertional fatigue, but also neuropsychological complaints including memory problems and inability to concentrate (DeLuca *et al.*, 1995; Moss-Morris *et al.*, 1996; Michiels and Cluydts, 2001). The exhaustion experienced by patients with CFS is hence not only physical but also mental in nature. Accordingly, it is conceivable that the CNS is involved in the pathophysiology of CFS (MacHale *et al.*, 2000; Afari and

Buchwald, 2003; Georgiades *et al.*, 2003; Schmaling *et al.*, 2003). More specifically, it has been suggested that the considerable motor slowing and persistent motor fatigue observed in CFS patients (Prasher *et al.*, 1990; Gaudino *et al.*, 1997; Marshall *et al.*, 1997; Vercoulen *et al.*, 1998) can arise from alterations in the cerebral motor system (Davey *et al.*, 2003). To date, there has been some indication that CFS may be associated with impaired excitability of cortical motor areas (Starr *et al.*, 2000; Davey *et al.*, 2003), but the evidence is mixed (Davey *et al.*, 2001; Zaman *et al.*, 2001). Furthermore, these previous studies have focused on cortico-spinal excitability, neglecting the remaining

extensive cerebral network supporting movement planning (Toni *et al.*, 2002b; de Lange *et al.*, 2004).

The aim of this study was to investigate the behavioural and neural correlates of movement planning in CFS patients, given that altered preparatory activity might account for several symptoms of this complex syndrome. To test this hypothesis, we used event-related functional MRI (fMRI) to examine brain activity in a sample of CFS patients and a matched sample of healthy controls (HC) during performance of two cognitive tasks, a motor imagery task (Parsons, 1994) and a visual imagery task (Shepard and Cooper, 1982). We used motor imagery to induce activity in cerebral structures directly involved in movement planning (Jeannerod, 1994; Kosslyn *et al.*, 2001), thus assessing motor planning independently from actual movement execution (Decety *et al.*, 1994; Parsons *et al.*, 1995; Porro *et al.*, 1996; Deiber *et al.*, 1998; de Lange *et al.*, 2004). We compared behavioural performance and neural activity directly across tasks, testing for differences between groups specifically related to performance of visual and motor imagery. Finally, the event-related design allowed us to (*post hoc*) sort trials and fMRI signals into correct, incorrect and missed responses. In this way, we could test for between-groups differences in error processing.

Methods

Subjects

Sixteen right-handed female CFS patients and 16 age-, gender- and education-matched healthy controls participated in the study after giving written informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands).

The age inclusion criterion was between 20 and 45 years. All patients and control subjects were assessed by means of detailed history and investigation, standardized psychiatric evaluation (SCID-I) and computer assessment of questionnaires. Their physical activity pattern was assessed by actometer measurements during 2 weeks. All patients conformed to US Center for Disease Control and Prevention criteria for CFS (Fukuda *et al.*, 1994). Subjects who manifested psychiatric comorbidity (e.g. depression) were excluded from the study. Demographic features and scores of questionnaires assessing CFS-related features such as fatigue, pain, sleep difficulties and cognitive impairment of the groups are described in Table 1.

Tasks

The subjects participated in alternating blocks of visual imagery (VI) and motor imagery (MI), each block consisting of eight stimuli. During VI, subjects were shown typographical characters (F, G, J and R) and their mirror images. Each stimulus could be rotated from its upright position (0°) in 30° steps until 180°, generating a set of 56 stimuli. These stimuli were serially presented to the subjects in a random order. The subjects had to report whether the displayed typographical character was a canonical letter or its mirror image, regardless of its rotation (Fig. 1, lower row). During MI, subjects were shown four different line drawings of hands (left or right hand, viewed either from the back or from the palm) or their mirror images. The same rotations and display procedures described for VI were used for MI. The subjects had to report whether the displayed hand drawing was a

Table 1 Mean (SD) of demographic features and CFS screening measurements of patients and healthy controls

	CFS	HC
Demography		
Female/male participants	16/0	16/0
Age (years)	28.4 (6.0)	24.9 (6.4)
Educational attainment (1–7)*	4.6 (1.1)	4.9 (1.7)
CFS screening measurements [†]		
Duration of CFS (years)	6.3 (4.4)	0 (0)
CIS-R		
Fatigue (8–56)*	51.9 (4.2)	16.1 (7.0)
Reduced concentration (5–35)*	29.6 (4.5)	12.1 (5.5)
Reduced motivation (4–28)*	17.3 (6.6)	6.5 (2.7)
Reduced activity (3–21)*	16.1 (4.0)	5.3 (2.5)
SIP-8 total (0–9937)*	1573 (671)	27 (36)
SCL-90 (90–450)*	164.3 (46.8)	102.2 (8.9)
BDI (0–63)*	14.6 (8.3)	1.6 (1.7)
BDI-primary care (0–21)*	3.6 (3.6)	0.4 (0.6)
Mean actometer score	61.1 (16.2)	74.2 (22.6)

*Range of the scale; [†]In two cases in the HC group, these measures were not obtained and they are not included. For all questionnaires, the possible range is given in parentheses. CIS-R = revised checklist individual strength; SCL-90 = symptom checklist 90; SIP = sickness impact profile.

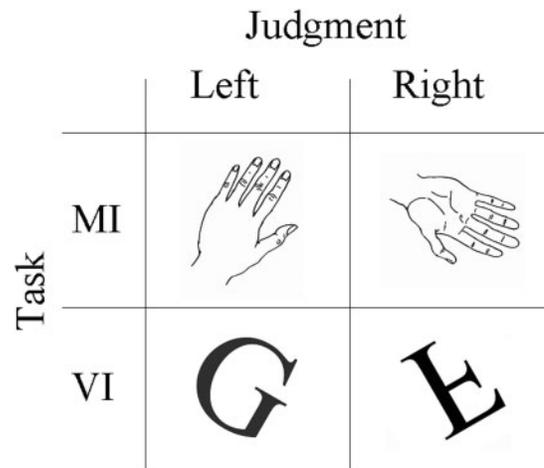


Fig. 1 Task set-up. Examples of stimuli used in the MI and VI tasks. During MI, subjects had to discriminate between left and right hands, regardless of the orientation of the stimulus, by pressing either the left or right button on a button box with the index or middle finger of their right hand. During VI, subjects had to discriminate between canonical (left button) and mirror images (right button) of letters, regardless of the orientation of the stimulus. Stimuli were serially presented one by one in randomized orientation within each task block.

left or a right hand, regardless of its rotation (Fig. 1, upper row). After practising the tasks both outside and inside the scanner, subjects were scanned during task performance for ~40 min. During scanning, subjects responded by pressing one of two buttons on a MR-compatible button box, which was positioned in their right hand. Responses were measured in the scanner for subsequent behavioural analysis. Each trial started with the presentation of a fixation cross (baseline) for a variable interval (0.75–1.25 s), followed by a visual stimulus (a typographical character or a drawing of a hand). When a response

was provided, the visual stimulus was replaced by the baseline fixation cross until the presentation of the next visual stimulus. The intertrial interval (ITI) was adjusted to task performance in order to balance the time spent off-task across experimental conditions (off-task time designates the temporal intervals interposed between a behavioural response and the next stimulus presentation). We adjusted the ITI according to the formula:

$$\text{ITI} = C + R$$

where: $C = 2.0$ s (VI) or 2.5 s (MI); and R is dependent on the angle of the stimulus ($R = \alpha/180$ s where α is the stimulus rotation in degrees).

Stimulus rotation was randomized from trial to trial. At the end of each block, the baseline fixation cross was presented for 20 s. The start of the next block of trials was announced by a transient change in size of the fixation cross.

MRI acquisition and analysis

Functional images were acquired on a Siemens (Erlangen, Germany) SONATA 1.5 T MRI system equipped with echo planar imaging (EPI) capabilities and using the standard head coil for radio frequency transmission and signal reception. Blood oxygenation level-dependent (BOLD) sensitive functional images were acquired using a single shot gradient EPI-sequence [TE (echo time)/TR (repetition time) = 40/2560 ms; 32 axial slices, slice thickness = 3.5 mm; FOV (field of view) = 224 mm]. High-resolution anatomical images were acquired using a MP-RAGE sequence (TE/TR = 3.93/2250 ms; voxel size = $1.0 \times 1.0 \times 1.0$ mm, 176 sagittal slices; FOV = 256 mm).

Functional data was analysed with SPM99 (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm) in the context of the General Linear Model (GLM). Prior to analysis, functional images were realigned, slice-time corrected, normalized and smoothed using a 10 mm full-width at half maximum isotropic Gaussian kernel. By jittering trial onsets with respect to image acquisition and by randomizing stimulus rotations on a trial-by-trial basis, our experimental design allowed for an event-related analysis of the fMRI time series.

The analysis considered main effects of task (MI, VI) as well as the linear and quadratic effects of stimulus rotation (from 0° to 180° in 30° steps). Correct, incorrect and missed responses were modelled separately and included in the model. Trial-by-trial reaction time (orthogonalized to task and rotation components) and head-related movement regressors were incorporated as confounds in the model (see de Lange *et al.*, 2004).

We report the results of a random effects analysis on clusters surviving correction for multiple comparisons ($P < 0.05$) (see Friston *et al.*, 1996). Parameter estimates (i.e. regression coefficients, in the context of the present multiple regression analysis) were calculated for these contrasts. Note that, although indicative of effect size, the absolute values of parameter estimates do not convey meaning, since they have to be interpreted in relation to the scaling of the covariate (Friston *et al.*, 1996).

Behavioural analysis

Mean response times (RTs), error rates (ERs) and missed responses were calculated for each level of the two experimental factors (task, rotation) for each group (CFS, HC). A three-way ($2 \times 2 \times 7$) ANOVA (analysis of variance) was carried out to examine the effects of group (CFS, HC), task (MI, VI), and rotation (0° to 180° in 30° steps) on RT. To investigate experimental effects on error and/or miss rate, we carried out a MANOVA (multiway analysis of variance) considering the effects of group (CFS, HC) and task (MI, VI) on

ERs and rate of missed responses. Subjects were considered as a random factor. Alpha-level was set at $P < 0.05$ and, where applicable, Greenhouse-Geisser corrected. To assess possible fatigue and/or practice effects during the scanning session, we calculated the regression of RTs over scanning time for each subject and for each task. A negative regression slope would point to a practice effect (RTs become shorter over time). A positive slope would point to a fatigue effect, indicating that the subjects become slower over time. Differences in regression slope between groups (CFS, HC) and tasks (MI, VI) were assessed by means of a two-way ANOVA.

Results

Subject characteristics

Table 1 gives an overview of demographic data of CFS patients and HC subjects. All subjects were female. Groups did not differ in age [$F(1,30) = 2.60$; $P = 0.12$] or educational attainment [$F(1,30) = 0.37$; $P = 0.55$]. CFS patients reported significantly higher levels of fatigue, experienced more concentration problems and a reduced motivation than HC, as indexed by the checklist individual strength (CIS-R, see Table 1). Sickness impact profile (SIP) scores indicated that the disorder had a significant impact on their quality of life (scores between 1200 and 2200 denote a severe impact on the quality of life). There was a trend of mean actometer difference between groups [$F(1,28) = 3.36$; $P = 0.078$], suggesting that CFS patients were physically less active during the 2 weeks preceding the scanning session than their healthy counterparts. Although the scores of Beck Depression Inventory (BDI) were elevated to the range of mild depression in the CFS group, this cannot be readily interpreted as an indication of mild depression in this group due to the somatic nature of several BDI items. We therefore employed a subset of the BDI questionnaire, the BDI-Primary Care, as a screening instrument (Beck *et al.*, 1997). The items of this subset are much less prone to being confounded by somatic symptomatology.

Behavioural performance

Figure 2 illustrates the mean RT as a function of rotation during MI and VI for CFS and HC. A three-way ($2 \times 2 \times 7$) ANOVA was carried out to examine the effects of task (MI versus VI), group (CFS versus HC) and rotation (0° to 180° in 30° steps) on RT. This revealed a significant effect of task [$F(1,15) = 122.4$; $P < 0.001$], rotation [$F(6,10) = 52.2$; $P < 0.001$], group [$F(1,15) = 21.8$; $P < 0.001$] and a task \times rotation interaction [$F(6,10) = 5.4$; $P = 0.01$]. There were no significant group \times task [$F(1,15) = 0.4$; $P > 0.5$] or group \times rotation [$F(6,10) = 2.33$; $P = 0.11$] interactions.

Table 2 reports the mean rate of errors and misses for the CFS and HC groups. There were no differences in error rate between groups during MI [$F(1,30) = 1.08$; $P = 0.31$] and VI [$F(1,30) = 1.42$; $P = 0.24$]. However, the CFS group showed a larger number of missed responses than the HC group during MI [$F(1,30) = 6.26$; $P = 0.018$] and VI [$F(1,30) = 7.01$; $P = 0.013$].

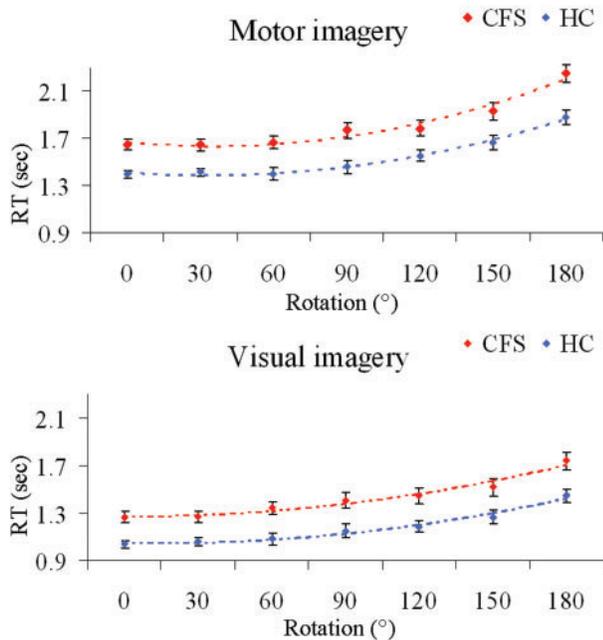


Fig. 2 Behavioural results. Mean RT (in s) \pm standard error of the mean (SEM) as a function of rotation during MI and VI for CFS patients and healthy controls. Dashed lines represent regression curves between RT and orientation. CFS patients are considerably slower than HC in both tasks, but the two groups carried out the mental rotations at comparable speed. RT increased as a function of rotation in both CFS and HC groups, indicating that both patients and healthy controls were effectively engaged in task performance.

Table 2 Mean (SD) percentage of errors and misses across groups and imagery types

	CFS		HC	
	MI	VI	MI	VI
Errors (%)	8.0 (4.0)	6.9 (5.3)	6.3 (4.8)	4.8 (4.6)
Misses (%)	4.8 (5.8)	5.2 (5.6)	1.1 (1.1)	1.3 (1.6)

To check for differences in performance over time, we carried out an ANOVA examining task (MI versus VI) and group (CFS versus HC) differences in the regression of RTs over scanning time. Both groups showed similar negative regression slopes across conditions, with considerable variability [HC: mean (SD) = -0.88 (0.94); CFS: mean (SD) = -0.61 (1.13)]. There were no differences in slope between groups [$F(1,60) = 1.02$; $P = 0.32$] or tasks [$F(1,60) = 0.43$; $P = 0.52$], suggesting that there was no differential fatigue and/or practice effect between tasks or groups.

Neural activity

Our experimental design allowed for a direct comparison between task-related neural activity in CFS patients and matched healthy controls, in the context of both common neural activity across tasks (designated by ' \cap '; e.g. 'MI \cap VI') and differential neural activity between tasks, i.e. greater

neural activity during one task than the other (designated by '>'; e.g. 'MI > VI'). Furthermore, we could distinguish between task-related and rotation-related neural responses, as detailed in Methods. Finally, the event-related design allowed us to (*post hoc*) sort trials and fMRI signals into correct, incorrect and missed responses. Stereotactic coordinates (Talairach and Tournoux, 1988; Evans *et al.*, 1994) of regions showing significant differences between groups across task and rotation, as well as error-related activities, are listed in Table 3.

There was extensive spatial overlap of task-related neural activity across groups. Figure 3 shows two examples of highly similar neural responses across CFS and HC groups in the left posterior parietal and dorsal premotor cortex. In this paper, however, we focus on differences in neural activity between CFS patients and the HC group. The details of task- and rotation-related responses evoked in a different cohort of healthy subjects are discussed in a separate report (de Lange *et al.*, 2004).

During both tasks, the caudate nucleus was more strongly activated in the HC group than in the CFS group, bilaterally. Conversely, the calcarine fissure was significantly more activated in the CFS group than in the HC group (across tasks). The calcarine activity was within the variability range (8 out of 10) of cytoarchitectonically defined V1 (Amunts *et al.*, 2000). Differences in increases of neural activity with increasing rotation between groups were observed in the inferior occipital sulcus and in the declive of the cerebellum (Schmahmann *et al.*, 1999) (Fig. 4). The occipital cluster falls near the location of hMT + IV5, the human visual motion complex (Amedi *et al.*, 2002). The cerebellar cluster is located near the site of previously reported saccade-related responses (Hayakawa *et al.*, 2002). During MI, these occipital and cerebellar clusters show a steeper increase in activity as a function of rotation in the CFS group than in HC. The opposite pattern is observed during VI.

Analysis of error-related activity revealed differential activity between groups in a ventro-rostral portion of the cingulate sulcus ($-8, 32, 30$; $Z = 4.03$; cluster size = 198 voxels; Fig. 5C and D), falling on the anterior rostral cingulate zone as defined by Picard and Strick (1996) and within the 'affective division' of the anterior cingulate cortex (ACC) delineated by Bush *et al.* (2000). This ventro-rostral region was activated during errors in the HC group, but not in the CFS group. This region was clearly distinct from the region activated in both groups during error trials (Fig. 5A and B). This portion of the anterior paracingulate sulcus ($-2, 16, 56$; $Z = 6.40$; cluster size = 5992 voxels; Paus *et al.*, 1996) falls on the posterior rostral cingulate zone (Picard and Strick 1996) and within the 'cognitive division' of the ACC (Bush *et al.*, 2000), near ACC fields involved in error detection and the online monitoring of performance (Carter *et al.*, 1998; Kiehl *et al.*, 2000).

Discussion

In this study, we investigated brain activity of a sample of CFS patients and matched healthy controls with event-related fMRI

Table 3 Task-related, rotation-related and error-related activities for common (\cap) and differential ($>$) effects across groups and imagery types

Factor	Functional comparison	Group comparison	Anatomical region	Hemisphere	Z score	Cluster size	Stereotactic coordinates		
Task	MI \cap VI	HC $>$ CFS	Caudate nucleus	L	4.33	268	-16	-10	24
				R	4.53	185*	20	16	16
Rotation	MI $>$ VI	CFS $>$ HC	Calcarine fissure	L	4.13	290	-18	-56	2
		CFS $>$ HC	Cerebellum (declive)	L	4.56	155*	-18	-64	-24
			Inferior occipital sulcus	R	4.22	495	30	-70	-2
Errors	MI \cap VI	HC $>$ CFS	Ventral anterior cingulate	L	4.03	198	-8	32	30

Only contrasts that yielded significant ($P < 0.05$ corrected for search volume) between-group differences are reported. Significant trends ($P < 0.10$ corrected for search volume) are marked with an asterisk.

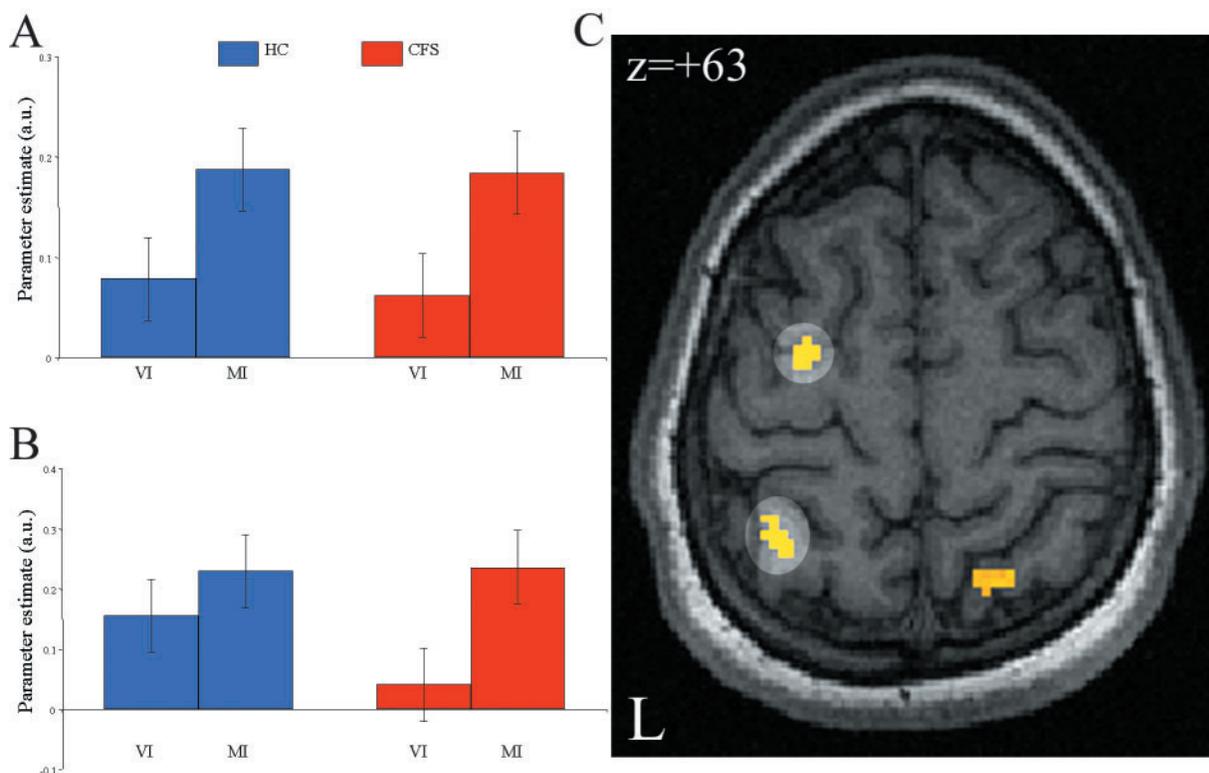


Fig. 3 Common increases in neural activity with increasing rotation. Anatomical location and effect size of two regions that increase their activity more during MI than during VI as a function of stimuli rotation, both in CFS patients and healthy controls. Effect size (parameter estimates \pm SEM, in arbitrary units) of the explanatory variable ‘rotation’ is plotted for HC (blue) and CFS (red) groups, and for MI and visual imagery VI separately. (A) Left dorsal premotor cortex ($-26, -8, 62$; upper cluster on anatomical image) and (B) left posterior parietal cortex ($-30, -54, 64$; lower cluster on anatomical image). (C) The activations are overlaid on a high-resolution anatomical image. In both regions and both groups, neural activity increased with increasing rotation. The increase was greater during MI than VI. a.u. = arbitrary units.

during a motor imagery and a control visual imagery task, while monitoring their behavioural performance. All CFS patients reported significantly higher levels of fatigue, experienced more concentration problems and a reduced motivation than HC, and CFS significantly affected their quality of life. Furthermore, CFS patients were physically less active than HC as indicated by actometer measures collected over 2 weeks. These findings are in line with previous studies investigating physical activity patterns (van der Werf *et al.*, 2000) and

behavioural measures (Prins *et al.*, 2001) in groups of CFS patients. In the following sections, we discuss behavioural and neural effects of our experimental manipulation, and their relevance for pathophysiological models of this illness.

Behavioural findings

Both groups were able to perform MI and VI tasks with low (<8%) error rates (Table 2), indicating that CFS as well as HC

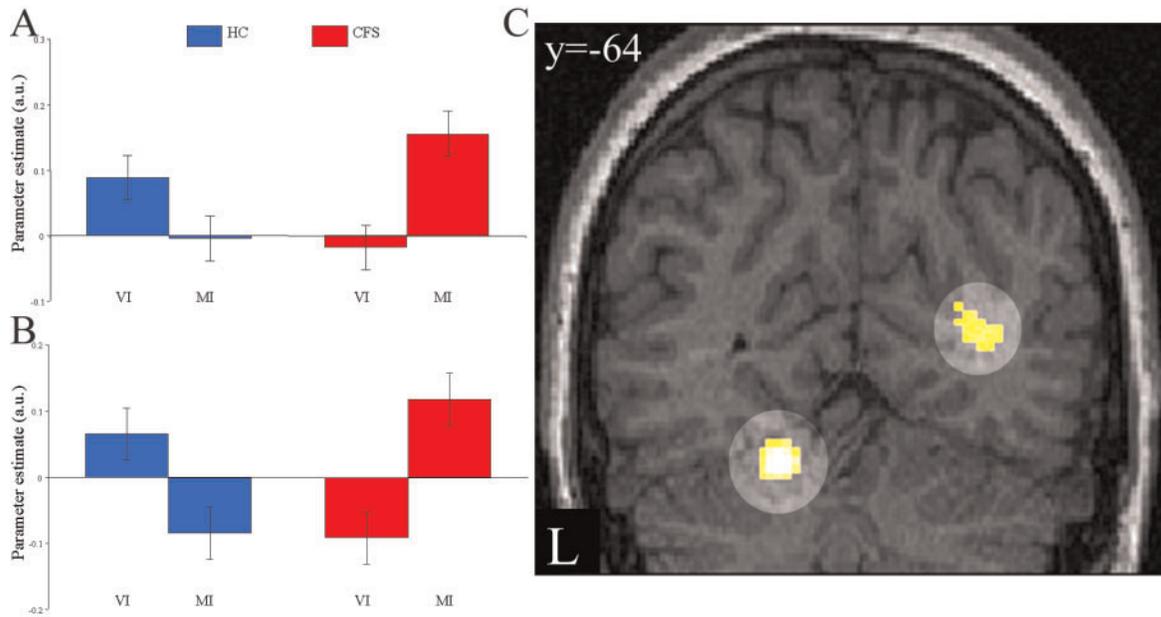


Fig. 4 Differential increases in neural activity with increasing rotation. Anatomical location and effect size of two regions with differential responses in CFS patients and healthy controls. Effect size (parameter estimates \pm SEM, in arbitrary units) of the explanatory variable rotation is plotted for HC (blue) and CFS (red) groups, and for MI and VI separately. (A) Cerebellar declive ($-18, -64, -24$; left cluster on anatomical image) and (B) inferior occipital cortex ($30, -70, -2$; right cluster on anatomical image). (C) The activations are overlaid on a high-resolution anatomical image. In both regions, there was a stronger increase in activity as a function of rotation in the CFS patients than in HC during MI, but the opposite pattern was present during VI.

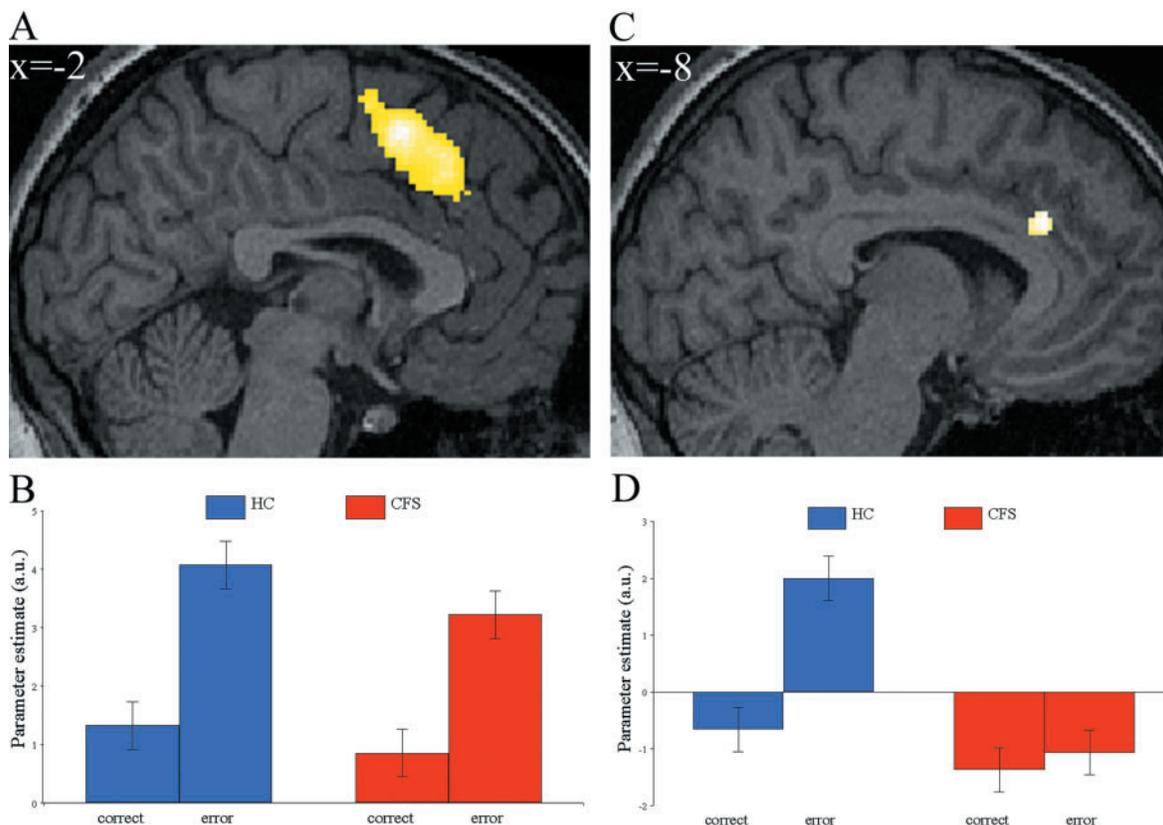


Fig. 5 Error-related neural activity. Anatomical location and effect size (parameter estimates \pm SEM, in arbitrary units) of error-related activity for CFS patients and healthy controls. (A) Anatomical location and (B) effect size of common error-related responses across CFS and HC groups along the paracingulate sulcus ($-2, 16, 56$). (C) Anatomical location and (D) effect size of differential error-related responses between CFS and HC groups along the cingulate sulcus ($-8, 32, 30$). a.u. = arbitrary units.

subjects were effectively solving the tasks. Error rates between the two groups did not differ, but CFS patients were significantly slower (Fig. 2), resulting in more missed responses (Table 2). It might be argued that the higher number of missed responses in the CFS group reflects slowed information processing. For instance, CFS patients respond slowly to instruction cues in terms of both reaction times and movement times (Prasher *et al.*, 1990; Gaudino *et al.*, 1997; Marshall *et al.*, 1997). However, CFS patients are slow not only during choice reaction time tasks, but also in simple reaction time tasks (Vercoulen *et al.*, 1998; Davey *et al.*, 2001). Therefore, slow performance appears to arise from specific problems in dealing with motor processes associated with response preparation (Davey *et al.*, 2003) rather than with general problems in processing complex information. This inference is supported by recent electrophysiological studies showing that, in CFS patients, both reaction and movement times directly correlate with corticospinal excitability (Davey *et al.*, 2003), and the slowing of simple reaction times parallels the reduction of frontal readiness potentials (Gordon *et al.*, 1999). On the basis of these findings, it is conceivable that the increased reaction times observed in both imagery tasks in the CFS group were due to impaired motor processes rather than to problems with complex information processing.

Reaction time increased with increasing stimulus rotation, indicating that both groups of subjects used mental rotation to judge the laterality of hands (MI) and letters (VI). The rotation-related modulation of RT differed across tasks (task \times rotation interaction), indicating that mental rotation in MI engaged additional resources compared with VI. Crucially, although CFS patients were slower than HC, the mental rotations that were required to perform the task were done with the same speed in both groups, as shown by the parallel curves relating reaction times with rotation (Fig. 2).

Neural data

Our experimental design allows us to dissociate the overall speed of task performance (indexed by the offset of the reaction time curves) from the specific speed of mental rotation (indexed by the slope of the reaction time curves). Analogously, the neural data collected in our subjects can also be dissociated into general task-related neuronal responses and rotation-related neuronal responses. The former may be informative with respect to the overall slowing of the CFS patients, whereas the latter allows inferences about specific differences in the neural implementation of the motor and visual imagery tasks between CFS and HC groups.

Neural findings—task-related responses

CFS patients showed less task-related activity in the caudate nuclei than HC across both MI and VI. This region has been repeatedly implicated in selecting a response given a specific context (Hikosaka, 1993; Passingham, 1993; Houk and Wise, 1995; Jueptner and Weiller, 1998), possibly by merging

mesencephalic reward signals with cortical sensori-motor representations (Jog *et al.*, 1999; Lauwereyns *et al.*, 2002; Toni *et al.*, 2002a). In neurological terms, Chaudhuri and Behan (2000) have recently suggested that striatal disturbances might constitute a pathogenic mechanism of central fatigue (in contrast to peripheral neuromuscular fatigue), disconnecting motivational signals from the cortico-striatal-thalamo-cortical loops. Our results appear consistent with this framework, although it remains to be seen whether the reduced striatal responses observed in CFS patients are related to a local impairment or rather to reduced input from ventral cingulate regions (see below).

During both tasks, CFS patients showed stronger BOLD responses than healthy controls along the calcarine sulcus (putative V1; Table 3). This difference in V1 responsiveness between groups is likely due to a difference in presentation time of the visual stimuli between CFS and HC cohorts. Since CFS patients produced longer RTs than HC, and stimuli disappearance was time-locked to subjects' responses, it follows that CFS patients experienced longer visual presentations than HC. The difference in BOLD signal was present across both MI and VI tasks, consistent with the fact that CFS patients were (equally) slower during both tasks (Fig. 3).

Neural findings—rotation-related responses

Both HC and CFS groups showed stronger increases in neural activity during MI than during VI in left posterior parietal and dorsal premotor cortex, in line with previous findings (de Lange *et al.*, 2004) and suggesting that mental simulation of actions was playing a role in both groups during the MI task. During MI, CFS patients showed stronger rotation-related BOLD increases than HC along the cerebellar declive and occipito-temporal cortex (Fig. 3). The latter differential response falls close to the human visual motion complex (hMT + /V5; see Amedi *et al.*, 2002). This cortical region is involved in processing visual motion (Nichols and Newsome, 2002), either real (McKeefry *et al.*, 1997; Sunaert *et al.*, 2000) or imagined (Tootell *et al.*, 1995; de Lange *et al.*, 2004). The stronger rotation-related increase in signal found in this visual field when CFS patients were engaged in motor imagery suggests that this cohort might have solved the task by relying on visual processes more heavily than the HC group. It remains to be seen whether the neural effect we observed is related to a voluntary strategic bias or rather to an automatic compensatory process.

A second cluster of rotation-modulated responses differentially expressed by the two groups falls in the declive of the cerebellum, which is implicated in execution of saccades (Noda and Fujikado, 1987; Hashimoto and Ohtsuka, 1995; Hayakawa *et al.*, 2002). It is reasonable to interpret the stronger rotation-related increase in BOLD signal observed during MI in the CFS patients (Fig. 5) in terms of different patterns of eye movements between the two groups. Given the relevance of eye movements for performance of visual imagery tasks

(Laeng and Teodorescu, 2002), it is conceivable that the stronger and MI-specific modulation of cerebellar activity found in CFS patients support the suggestion that this cohort might have solved the motor imagery task by using visual imagery rather than first-person kinaesthetic processes (Jeannerod, 1994).

Neural data—error processing

CFS patients as well as HC showed robust error-related activity along the mesial aspects of dorsal frontal cortex, during both tasks (Fig. 5A and B). This region has been repeatedly involved in error processing (Carter *et al.*, 1998; Kiehl *et al.*, 2000; Holroyd and Coles, 2002; Holroyd *et al.*, 2002), and the present results indicate that there are no differences in CFS patients with respect to the functionality of this neural component of the human error-processing system. Conversely, there were inter-group differences during error trials in a neighbouring but distinct cortical region, namely the ventral portion of the cingulate gyrus (Fig. 5C and D). This region showed strong responses during error trials in HC, but was not responsive in CFS patients during the same type of trials. Bush *et al.* (2000) suggest a functional dissociation between dorsal and ventral portions of the ACC. While the dorsal (or ‘cognitive’) ACC is thought to be involved in attentional modulations, error detection and working memory, the ventral (or ‘affective’) ACC is thought to be involved in assessing the salience of emotional/motivational information and in the regulation of emotional responses (Bush *et al.*, 2000). As an example of a disturbance of the latter system, a patient with lesions along orbital and lower mesial frontal cortices appeared to be ‘apathetic and unconcerned when significant events occur, such as making mistakes’ (Eslinger and Damasio, 1985). Our findings indicate that CFS patients lack error-related responses in this affective portion of the ACC. It remains to be seen whether prolonged perception of fatigue reduces motivation, and thus ventral ACC responses, or whether a reduction of ventral ACC activity plays a causal role in the aetiology of CFS, decreasing motivational drive and increasing perception of fatigue. A possible way of distinguishing between these two possibilities would be to use the present imaging protocol and test for dissociations between changes in symptomatology, behavioural responses and cerebral activity during the course of treatments affecting CFS symptomatology (Prins *et al.*, 2001).

Conclusions

We observed a general slowing of reaction times when CFS patients performed two different mental rotation tasks. This behavioural effect had a neural counterpart in reduced BOLD responses from the caudate nucleus. This finding is consistent with the hypothesis that striatal disturbances might constitute a pathogenic mechanism of central fatigue (Chaudhuri and Behan, 2000). CFS patients and HC solved the motor imagery problem with similar mental rotation speed and error rates. In neural terms, both groups used largely overlapping cerebral resources, namely parietal and precentral areas known to

support movement preparation (Thoenissen *et al.*, 2002; de Lange *et al.*, 2004). However, the CFS cohort solved the motor imagery task by recruiting additional cerebral regions supporting visual processes. This neural effect suggests that the CFS patients might have relied on visual imagery to compensate for a dysfunctional motor planning. In this perspective, the lowered levels of physical activity observed in the CFS population (van der Werf *et al.*, 2000) could be interpreted as an outcome of such dysfunctional motor planning. An alternative possibility is that the recruitment of additional visual resources in CFS patients represents a strategy driven by altered perception of effort (Fry and Martin, 1996), despite a functioning cerebral motor system.

Our neural data also indicate that, in the CFS cohort, the ventral ACC was not responsive during erroneous trials. This finding points to motivational disturbances as a crucial aspect of CFS. Taken together, our results confirm the multidimensional nature of CFS (Afari and Buchwald, 2003), highlighting cognitive and neural components of this illness.

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