Neural correlates of the chronic fatigue syndrome—an fMRI study

Floris P. de Lange, Joke S. Kalkman, Gijs Bleijenberg, Peter Hagoort, Sieberen P. vd Werf, Jos W. M. van der Meer and Ivan Toni

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

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 (Jeanne Rod, 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 historical and psychiatric 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 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

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

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

<table>
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<tr>
<th>MI</th>
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<td>Judgment</td>
<td></td>
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<td>Left</td>
<td></td>
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<td>Right</td>
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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 interpolated between a behavioural response and the next stimulus presentation). We adjusted the ITI according to the formula:

\[
\text{ITI} = C + R
\]

where: \(C = 2.0 \text{ s (VI)} \) or \(2.5 \text{ s (MI)}\); and \(R\) is dependent on the angle of the stimulus \(\text{R} = \alpha/180 \text{ s} \) where \(\alpha\) 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 1.5T 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 \(\text{TE (echo time)/TR (repetition time) = 40/2560 ms; 32 axial slices, slice thickness = 3.5 mm; FOV (field of view) = 224 mm}\). High-resolution anatomical images were acquired using a MP-RAGE sequence \(\text{TE/TR = 3.93/2250 ms; voxel size = 1.0 \times 1.0 \times 1.0 mm, 176 sagittal slices; FOV = 256 mm}\).

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).

**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 larger number of missed responses than the HC group during MI \([F (1,30) = 6.25; P = 0.018]\) and VI \([F (1,30) = 7.01; P = 0.013]\).
motor imagery CFS HC

Visual imagery CFS HC

Fig. 2 Behavioural results. Mean RT (in s) ± 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

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<tr>
<td></td>
<td>MI</td>
<td>VI</td>
<td></td>
<td>MI</td>
</tr>
<tr>
<td>Errors (%)</td>
<td>8.0 (4.0)</td>
<td>6.9 (5.3)</td>
<td>6.3 (4.8)</td>
<td>4.8 (4.6)</td>
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<tr>
<td>Misses (%)</td>
<td>4.8 (5.8)</td>
<td>5.2 (5.6)</td>
<td>1.1 (1.1)</td>
<td>1.3 (1.6)</td>
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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 ‘∩’; e.g. ‘MI ∩ 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 decline of the cerebellum (Schmahmann et al., 1999) (Fig. 4). The occipital cluster falls near the location of hMT+/V5, 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
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 ± 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 ± 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.
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 decline 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 supports 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 intergroup 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.

**Acknowledgements**

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**References**


