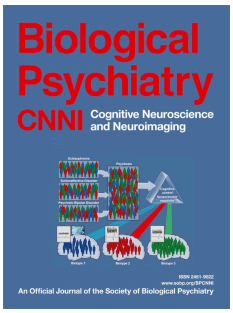
Accepted Manuscript



Fatigue is associated with altered monitoring and preparation of physical effort in patients with chronic fatigue syndrome

Marieke E. van der Schaaf, Karin Roelofs, Floris P. de Lange, Dirk EM. Geurts, Jos WM. van der Meer, Hans Knoop, Ivan Toni

PII: S2451-9022(18)30043-0

DOI: 10.1016/j.bpsc.2018.01.015

Reference: BPSC 247

To appear in: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*

Received Date: 8 November 2017

Revised Date: 9 January 2018

Accepted Date: 9 January 2018

Please cite this article as: van der Schaaf M.E., Roelofs K., de Lange F.P, Geurts D.E., van der Meer J.W., Knoop H. & Toni I., Fatigue is associated with altered monitoring and preparation of physical effort in patients with chronic fatigue syndrome, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2018), doi: 10.1016/j.bpsc.2018.01.015.

Fatigue is associated with altered monitoring and preparation of physical effort in patients with chronic fatigue syndrome.

Short Title: altered processing of effort in chronic fatigue

Marieke E. van der Schaaf[1,2], Karin Roelofs[2], Floris P de Lange[2], Dirk EM Geurts[5], Jos WM van der Meer[4], Hans Knoop[1,3], Ivan Toni[2]**

**shared senior authors*

[1] VU University Medical Center, Department of Medical Psychology, Expert Center for Chronic Fatigue, Amsterdam Public Health research institute, Amsterdam, the Netherlands

[2] Radboud University, Donders Institute for Brain, Cognition, and Behaviour, Nijmegen, The Netherlands
[3] Academic Medical Centre (AMC), University of Amsterdam, Department of Medical Psychology, Amsterdam, the Netherlands
[4] Radboud University Medical Centre, Department of Internal Medicine, Nijmegen, The Netherlands
[5] Radboud University Medical Centre, Department of psychiatry, Nijmegen, The Netherlands

Corresponding Author:

ME van der Schaaf, PhD
P.O. Box 9101, 6500 HB Nijmegen
The Netherlands
Telephone (+31) (0)24 3668236
Email: marieke.vanderschaaf@donders.ru.nl

Keywords:

- Psychosomatic symptoms
- Effort
- Functional MRI
- Prior beliefs
- Dorsolateral prefrontal cortex
- Supplementary motor area

Number of words:
Abstract: 237
Body: 4000
nr of figures: 5
nr of tables: 4
Number of supplementary materials:
9 (including 2 figures and 6 tables)

Abstract

Background: Chronic fatigue syndrome (CFS) is characterized by disabling fatigue, which is suggested to be maintained by dysfunctional beliefs. Fatigue and its maintenance are recently conceptualized as arising from abnormally precise expectations about bodily inputs and from beliefs of diminished control over bodily states, respectively. This study uses functional neuroimaging to identify the neural correlates of fatigue and its maintenance by beliefs during a physical effort task.

Methods: We isolate behavioural adjustments and cerebral activity during feedback processing and motor preparation, in the context of a task where CFS patients (N=85) and healthy controls (N=29) produced 30%, 50%, and 70% of their right hand maximal voluntary contraction (MVC), and received directional feedback on performance (e.g. “too little force”).

Results: CFS patients showed an effort-dependent behavioural bias towards less effort investment in response to directional feedback for the highest effort level as compared to HC. This bias was associated with reduced feedback-related activity in the DLPFC. These effects were proportional to state-related fatigue and prior beliefs about their ability to perform the task within CFS patients. CFS patients also showed higher activity in the supplementary motor area (SMA), proportional to their state-related fatigue, and reduced connectivity between SMA and sensorimotor cortex during motor preparation as compared to controls.

Conclusions: These findings link fatigue symptoms to alterations in behavioural choices on effort investment, prefrontal functioning and SMA connectivity, with the DLPFC being associated with prior beliefs about physical abilities.

Introduction

Chronic fatigue syndrome(CFS) is a disorder characterized by severe fatigue persisting for at least 6 months, leading to considerable impairment in daily functioning(1, 2). The pathogenesis of CFS is unknown, but several studies implicate neural mechanisms(3), as indicated by changes in cerebral volume(4-9) and functional alterations associated with cognitive processes, e.g. working memory, reward processing, error processing and fatigue provocation(10-16). However, it remains unclear whether and how those cerebral alterations relate to the key diagnostic feature of CFS, i.e. fatigue(1, 2) and how they explain the maintenance of maladaptive behaviours in CFS (e.g. reduced physical activity levels, sub-maximal performance on physical exercise tasks, and larger central activation failures during motor tasks)(17-21). This fMRI study therefore uses a physical force production task to objectively quantify behavioural and neural correlates of state-related fatigue, the key diagnostic feature of CFS(1,2), and its maintenance by dysfunctional beliefs.

Recent theoretic models have proposed that fatigue and its maintenance may be linked to two specific neurocomputational alterations. First, it is proposed that fatigue may arise when there is a discrepancy between prior expectations about the sensory consequences of actions and actual sensory inputs. Consequently, when prior expectations are overly precise, comparisons are systematically biased towards the prediction (prior). Second, it is proposed that this discrepancy is then explained away by higher-order regions. In the context of overly precise priors, this may serve to confirm fatigue beliefs, e.g. reduced force production abilities(22-24). This second hypothetical neurocomputational alteration fits with cognitive behavioural models of CFS(25-27) and clinical observations that dysfunctional beliefs are instrumental in maintaining fatigue-symptoms and behaviours in CFS(28-31). For instance, increased symptom perception has been linked to reduced expectations about physical abilities(32, 33) and to avoidance behaviours(34, 35). Following our preregistration(36), we therefore reasoned that alterations in this second neurocomputational process can be tested during the feedback evaluation of force productions. If the CFS brain explains away the discrepancy as evidence supporting the dysfunctional belief of reduced force production abilities(22, 23), this should lead to biased force adjustments towards producing less force in response to feedback, and this bias should be particularly strong when a large force is required. Accordingly, we used fMRI to measure brain activity during feedback about whole-hand movements at 30%, 50%, and 70% of maximal voluntary contraction, in a large cohort (N=85) of patients with CFS and healthy controls (HC, N=29), while muscle fatigue was avoided by using short bouts (~1 sec) of hand contractions. We test for the presence of a directional and effort-dependent bias

in behavioural and neural responses to performance feedback and its relation to fatigue and performance expectations in CFS patients, distinguishing this hypothesized neurocomputational alteration from a general disturbance in error processing previously observed in the ventral anterior cingulate cortex(vACC) of CFS patients(15).

Sub-maximal physical performance and central activation failures have been suggested to result from disturbances in pre-motor brain regions leading to an inability of centrally derived motor commands to produce the intended force outputs (19, 37). Based on recent literature, we argue that these effects result from the first neurocomputational alteration, involving the comparison of predicted/intended sensory consequences and actual sensory evidence. In addition, we propose that this comparison likely involves the SMA and its connectivity with sensorimotor regions during motor preparation. Supporting this, the supplementary motor area (SMA) has been associated with the generation of predicted sensory consequences of actions(22, 38, 39), and with the willingness to engage in effortful behaviour(40, 41). Moreover, a recent study showed that disruption of SMA with transcranial magnetic stimulation during motor preparation decreased effort perception(38), further supporting the role of this region in effort perception. Accordingly, we also explored whether CFS patients and HC differ in SMA activity and connectivity during motor preparation, and whether those neural metrics relate to subjective reports of fatigue and effort perception.

Methods

Participants

94 female CFS patients (meeting U.S. Centers for Disease Control (CDC)-criteria for CFS(2, 42), scoring ≥40 on the subscale fatigue of the checklist individual strength (CIS-fatigue)(43, 44), and ≥700 on the Sickness Impact Profile-8 (SIP8total)(45) and 30 gender, age and education matched healthy controls (<35 on CIS-fatigue and no chronic medical condition) were initially recruited for this study. See **supplement** and(36) for an overview of inclusion and exclusion criteria and study flowcharts. Fatigue (CIS-fatigue), functional impairment (SIP8total and SF-36), depressive symptoms (Beck depression inventory primary care, BDI-PC), disease duration, age and education level were assessed for clinical characterization of the CFS and control groups.

Task procedure

The task (**Figure1**) was programmed in Presentation (version 16.4, Neurobehavioral Systems, Inc), and presented on a screen that was visible via a mirror on the head coil in the MR scanner. The first visual cue was presented for 500 ms. This cue consisted of a vertical scale with graphical marker and a number below the scale ("30%", "50%", or "70%") indicating the desired force level that had to be achieved in that trial. The three force levels were proportions of each participant's MVC calibrated before the experiment (**Supplement**). After a jittered time interval (500-3500 ms, continuous uniform distribution), a "GO" instruction appeared on the screen for 1500 ms, instructing participants to apply the requested level of force on the handgrip for about 1 second (78% trials). After a second variable interval (500-3500 ms), visual feedback was provided for 500 ms indicating whether the squeeze was "correct", "too little" or "too much". In the remaining 12% of the trials, the initial cue was followed by a "NO SQUEEZE" instruction to dissociate neural activity related to motor preparation and execution. The next trial started after a jittered inter-trial-interval (1000-2500). In total, each participant performed 150 trials (50 per force level, randomized order), with a 20s break after the 75th trial, for a total task time of about 22 minutes. Feedback was based on a running average over the last ten trials of each force level, ensuring that actual probability of success was similar across subjects (44% "Correct", 25% "Too much" and 31% "Too little"). See **Supplement** for further details.

Subjective reports

State-fatigue, and task-induced fatigue and pain of the right hand were assessed at the onset of the experiment, immediately after practice and after the main experiment, using a zero-to-hundred visual analogue scale (VAS; 0=Not at all; 100=Very much). Experienced effort for each force level was assessed on the same VAS, before and after the experiment. State-fatigue was also assessed with the Profile of Moods State (POMS) questionnaire before and after the experiment. POMS and VAS reports of state-fatigue, providing multiple but correlated (CFS:r=.54; HC:r=.65) measures of state-fatigue, were combined into a single outcome parameter, by averaging across all VAS and POMS measures. Subjective reports were analyzed with a repeated measures ANOVA (rmANOVA; factors: time, group or time, force, group) in SPSS (IBM®, version21). Relations between these subjective reports and indexes of task performance and cerebral activity (see below) were assessed using two-tailed Pearson's correlation.

Beliefs about performance abilities

Participants' performance expectations were assessed before task performance, using the question "How much do you think you *will* squeeze for this force level", and a VAS (0-100, Too little–Too much) for each force level. Relations between prior beliefs and subsequent behavioural adjustments and cerebral activity (see below) were assessed using two-tailed Pearson's correlation.

The same VAS was used to assess the relationship between participant's perceived task performance after the experiment ("How much *did* you squeeze for this force level?") and the feedback received during the task (i.e. proportion "too little" versus "too much" - note that feedback was matched between groups).

Force adjustments

See **Supplement** for pre-processing details on the grip force data. We hypothesize that fatigue is associated with biased force adjustments towards producing less force following delivery of feedback (i.e. that CFS patients show less force increases after "too little" and/or more force decreased after "too much") and that this bias is particularly strong when a large force is required(36). Accordingly we calculated the adjustments in grip force following delivery of feedback(36) for each feedback type ("too little", "too much") and force level (30%, 50%, 70%). and analyzed these with a rmANOVA (factors: force, feedback, group).

To control for the ability to produce the force MVC was analyzed with rmANOVA (factors: time, group). To control for overall force delivery, average task-related force delivery was analyzed with rmANOVA (factors: force, group).

Neuroimaging data

After preprocessing (**Supplement**), individual fMRI timeseries were entered into a first-level general linear model considering 14 task regressors and 8 nuisance regressors (SPM12). Three regressors modelled the instruction period for each force level. (square waves starting at the onset of the instruction cue and ending at the onset of the ”GO/No-Squeeze” cues). Two regressors modelled force production (as a combination of a force-delivery regressor, i.e. square waves starting at the onset and with the duration of each force delivery event, and a force-magnitude regressor, i.e. a parametric modulation by the force produced). One regressor modelled the events occurring during the “No-Squeeze” trials. Nine regressors modelled the feedback events (“too little”, “correct” and “too much”, separately for each force level, as delta-functions time-locked to feedback onset). All events were convolved with a canonical hemodynamic response function. Contrasts capturing cerebral activity associated with feedback processing and motor preparation were taken to the second level and entered into two independent two-sample t-tests.

Group differences in feedback processing were assessed at the whole brain level, focused on feedback-related activity evoked on trials requiring 70% MVC (following behavioural results; contrast of incorrect vs correct trials). Based on previous findings on altered feedback-processing in the vACC of CFS patients(15), we also assessed group differences in feedback-related activity (70% trials) with a VOI analysis focused on this vACC (sphere of 8 mm radius centred at -8,32,30).

Based on recent literature showing that interference with the SMA reduces effort perception during a motor task(38), group differences in motor preparation were explored within a volume of interest (VOI), independently defined as a sphere of 8 mm radius centred on the mean MNI coordinates of the SMA region reported in(38)(xyz = -5, -10, 67). This region falls within the main effect of motor preparation (**TableS2**) and the anatomically defined SMA (using the Harvard–Oxford atlas http://www.cma.mgh.harvard.edu/fsl_atlas).

Functional Connectivity Analysis

Given the hypotheses that (i) fatigue perception involves chronic discrepancies between (overly precise) predictions of sensory inputs and the actual sensory inputs and (ii) that dysfunctional fatigue

beliefs result from 'explanation' of this mismatch by higher-order (metacognitive) regions that encode beliefs about subjective capacity for control, we further explored connectivity of the SMA with vACC/DLPFC during feedback and with sensorimotor cortex during motor preparation.

For each participant, physiological time series were extracted from an 8mm sphere centred on the individual peak effect within the main effect of motor preparation (**TableS2**) in the anatomically defined SMA. The scalar product of the physiological time series and the task time series was computed for the periods of motor preparation and for the periods of feedback (incorrect-correct for 30, 50 and 70%). These psycho-physiological interactions (PPI) were then added to new first level GLMs including the physiological time course, the task time course and the remaining task and nuisance regressors of the original GLM. Connectivity during feedback was assessed within the vACC (defined as above) and the bilateral DLPFC clusters showing group differences during feedback (see results). Connectivity during instruction was assessed in the sensorimotor cortex, defined as an 8 mm sphere centred around the region showing maximal activity during motor execution within the postcentral sulcus (xyz = -30,-32,50).

Statistical analyses

Statistical analyses were done in SPSS (IBM®, version 21) and correlation analyses were complemented with Bayes factors using JASP (jasp-stats.org, version 0.8.2.0). For neuroimaging data, statistical inferences are based on alpha-level of 0.05 with family-wise error correction for multiple comparisons, based on cluster-level statistics (for all whole-brain analyses, with cluster-forming threshold of P=0.001 ($p_{fwe\_wb\_cluster}$) or voxel-level statistics (for all VOI analysis(p_{fwe_VOI}), as recommended in(46). The alpha-level of the PPI analyses were Bonferroni corrected (p<.016) for the three VOIs.

Contrast maps will be made available upon request through the Donders Research Data Repository (data.donders.ru.nl).

Results

Clinical characteristics

Data were obtained on a sample of 85 CFS patients and 29 healthy controls (see **Supplement** and **figureS1** for details on exclusions). CFS patients had higher levels of clinical fatigue (CIS-fatigue: T_{112}=31.53, p<0.001), functional disability (SF-36: T_{112}=8.84, p<0.001), and depressive symptoms (BDI-PC: T_{112}=4.66, p<0.001) than HC (**Table1**). Groups did not differ in age (T_{112}=0.21, p=0.84), education level (T_{112}=0.33, p=0.75) or psychomotor speed (WAIS-dst: T_{112}=-1.50, p=0.14).

Subjective reports

State-fatigue **(Figure2A)** was higher for CFS patients than HC (main effect of group: $F_{2,111}$=144.4, p<0.001) and increased more in CFS patients after task performance (group by time interaction: $F_{2,111}$=6.54, p=0.012). Fatigue and pain in the right hand **(Figure2B/C)** was higher in CFS patients than HC (Fatigue: $F_{2,111}$=18.60, p<0.001; Pain: $F_{2,111}$=15.70, p<0.001) and increased more in CFS patients during the experiment (time by group interaction: Fatigue: $F_{2,111}$=4.78, p=0.009; Pain: $F_{2,111}$=10.8, p<0.001).

CFS patients reported, on average, higher effort levels than HC ($F_{1,112}$=21.17, p<0.001), but groups did not differ on task-related increases in effort (force by time interaction: $F_{2,111}$=4.60, p=0.011; group by time interaction: $F_{1,112}$=3.29, p=0.072, group by force by time interaction: $F_{1,111}$=1.69, p=0.187). Across both groups, higher force levels were experienced as more effortful (main effect of force: $F_{1,112}$=34.84, p<0.001; force by group interaction: $F_{2,111}$=2.67, p=0.072) and task-related increases in effort were larger for 30% and 50% than for 70% trials (force by time interaction: $F_{2,111}$=4.60, p=0.011; 30% vs 70% trials: T_{113}=3.03, p=0.003; 50% vs 70% trials: T_{113}=2.58, p=0.013)**(Figure2D)**.

Effort ratings correlated with state-fatigue within the control group (across effort levels: r=0.442, p=0.016, BF_{10}=3.59; 30% trials: r=0.003, p=0.99, BF_{10}=0.23; 50% trials: r=0.488, p=0.007 BF_{10}=7.19; 70% trials: r=0.573, p=0.001, BF_{10}=34.7) but not in the CFS group (across effort levels: r=0.106, p=0.334, BF_{10}=0.21; group interaction: $T_{3,110}$=-2.42, p=.017).

Force adjustments

In both groups, delivery of feedback indicating that too little force had been exerted was followed by an increase in force delivered in subsequent trials, and feedback indicating that too much force had been exerted was followed by a decrease in force (main effect of feedback: T_{112}=679.64,

p<0.001). The magnitude of these feedback-driven adjustments differed between groups as a function of force demands (group by force interaction: T_{112}=10.709, p<0.001): CFS patients (as compared to HC) showed smaller increases in force after a "Too little" feedback, and larger decreases after a "Too much" feedback during 70% trials (T_{112}=-2.65, p=0.009), but not during 50% trials (T_{112}=1.85, p=.067) or 30% trials (T_{112}=1.67, p=0.098; see **Figure3A**, **FigureS3**, **Table2**).

Pearson's correlation analysis within the CFS group revealed that, on 70% trials, larger negative biases (i.e. smaller force increases after "Too little" feedback than correspondingly decreases after "Too much" feedback) were associated with higher levels of state-fatigue (CFS: r=-0.26, p=0.015, BF_{10}=2.51; HC:r=.038, p=.85, BF_{10}=0.24; no group interaction: T=-.83, p=.41) and lower performance expectations (CFS:r=0.37, p<.001, BF_{10}=45.27; HC:r=.28, p=.14, BF_{10}=0.65; no group interaction: T=.41,p=.68) **(Figure3B/C)**. There were no significant correlations between the clinical trait variables (CIS-fatigue, SIP-total, SF-36 and disease duration) and behavioural adjustment bias within the CFS group (all p>.05).

There was no significant main effect of group ($F_{1,112}$=0.21, p=0.647) or group by time interaction ($F_{1,112}$=1.70, p=0.194) on MVC. Furthermore, MVC increased similarly in both groups during the experiment (main effect of time: $F_{1,112}$=15.19, p=0.001)**(Figure2E)**. On average, the two groups did not differ in the amount of force delivered during the task (T_{112}=0.72, p=0.473). There was a force by group interaction ($F_{2,111}$=8.01, p=0.002), with CFS patients delivering comparable force to HC during the 50% trials (T_{112}=0.98, p=0.33) and the 70% trials (T_{112}=-0.864, p=0.39), but not during the 30% trials, where patients exerted slightly (4%) more force (T_{112}=2.22, p=0.028). This deviation most likely reflects a difference in the acquired force-level during training, as it fell within the 8% range allowed for the acquisition of the force levels during training. (**Figure2F, Table3**).

Beliefs about performance abilities

We next assessed whether perceived performance assessed after the task ("How much *did* you squeeze") was predicted by actual feedback received during task or by expected performance assessed prior to the task. Perceived performance correlated with feedback received during the task (i.e. proportion "too little" versus "too much") in HC (r=-0.478, p=0.009; BF_{10}=6.12), but not in CFS patients (r=-0.146, p=0.185, BF_{10}=0.32), Instead, in CFS patients performance was more strongly associated with expected performance (CFS: r=0.24, p=0.029, BF_{10}=1.43; HC: r=0.26, p=0.172, BF_{10}=0.56), suggesting that CFS patients failed use task-feedback when judging their performance.

Neuroimaging data

Main task effects

Main task effects across both groups are summarized in **FigureS2** and **TableS2-S6**. The force production task evoked statistically-dissociable responses during motor preparation (including the premotor/supplementary motor cortex, bilateral anterior/dorsolateral prefrontal cortex and bilateral insula, extending to inferior prefrontal cortex) and motor execution (including left primary motor and somatosensory cortex and right cerebellum). During task feedback, higher activity for feedback indicating that the squeeze was correct versus incorrect was seen in medial orbitofrontal cortex and posterior cingulate cortex as well as in bilateral ventral putamen, nucleus accumbens and extending to the bilateral amygdala. Higher activity for feedback indicating that the squeeze was incorrect versus correct was seen in a network including the premotor cortex and bilateral inferior frontal gyrus. No group differences were observed during motor execution.

Group differences

The group difference in feedback-driven adjustments during 70% trials had a cerebral counterpart in reduced feedback-related activity in the bilateral middle frontal gyrus, covering Brodmann Area (BA) 9, BA8, BA6, and extending to the inferior frontal gyrus (BA44/45) for CFS patients versus controls. This effect (Left DLPFC: maximum at -48,14,46, T= 4.39, $p_{fwe\_wb\_cluster}$=0.006; Right: xyz=24,34,44, T=4.15, $p_{fwe\_wb\_cluster}$<0.001) pertained to feedback indicating that too little or too much force had been produced (**Figure 4A, Table 3**). No significant group differences were seen on feedback-related activity evoked during 50% and 30% trials. Pearson's correlation analysis within the CFS group revealed that reduced feedback-related DLPFC activity was associated with lower performance expectations (CFS: r=0.24, p=.027, BF_{10}=1.51; HC: r=.15,p=.43, BF_{10}=0.31; no group interaction), higher levels of state fatigue (CFS: r=-.24, p=0.024, BF_{10}=1.63; HC: r=.19,p=.34, BF_{10}=0.36; no group interaction) and larger behavioural adjustment biases on 70% trials (CFS: r=0.26, p=0.016, BF_{10}=2.33; HC r=.026,p=.89, BF_{10}=0.23; no group interaction) **(Figure4D-F)**. These findings are not explained by differences in feedback occurrences, which were matched across subjects and did not correlate with DLPFC activity (**Supplement**).

Analysis on extracted data from the vACC revealed reduced vACC activity in CFS patient relative to controls on 70% trials (T_{112}=-2.07, $p_{extracted}$=0.040) while no significant group differences were observed for 50% (T_{112}=-1.94, $p_{extracted}$=0.055) and 30% (T_{112}=0.15, $p_{extracted}$=0.88). This reduction was larger for 70% trials than for 30% trials (Group by force: $F_{1,112}$=4.46, $p_{extracted}$=0.037)**(Figure4C)**. There

were no correlations between feedback-related vACC activity and state fatigue (CFS: r=-0.062, p=0.57, BF_{10}=0.16; HC: r=.038,p=.84, BF_{10}=0.24; no group interaction), performance expectations (CFS: r=.019, p=.86, BF_{10}=0.16; HC:r=.26,p=.17, BF_{10}=0.56; no group interaction) or behavioural adjustment bias on 70% trials (CFS: r=0.039, p=0.72, BF_{10}=0.14; HC: r=.056,p=.77, BF_{10}=0.24; no group interaction) within the CFS or HC groups.

CFS patients showed stronger preparation-related activity within the SMA than HC (xyz=-4,-4,68, T=3.21, p_{fwe_VOI}=0.017; **Figure5A/B**, **Table3**). Within the CFS group, stronger preparation-related SMA activity was associated with higher levels of state-fatigue (across force levels: r=0.28, p=0.009, BF_{10}=4.01; 30% trials: r=0.238, p=0.032; 50% trials: r=0.27, p=0.012; 70% trials: r=0.32, p=0.003)**(Figure5C)**. No such relationship was observed in HC (across force levels: r =-.022, p=.91, BF_{10}=0.23; no group interaction: $T_{3,110}$=1.47, p=.15). Group difference in SMA activity did not simply reflect differences in force production as no significant associations were found between SMA activity and the amount of force delivered during the task, neither across force levels (r=-0.113, p=0.302) nor for each force level separately (30%: r=-0.143, p=0.191; 50%: r=-0.068, p=0.535; 70%: r=-0.067, p=0.542). Correlations between SMA activity and reported effort (CFS: r=-0.11, p=0.34, BF_{10}=0.21; HC: r=.13, p=.50, BF_{10}=0.29; no group interaction) or performance expectations (CFS: r=.01, p=.95, BF_{10}=0.22; HC: r=-.017, p=.38, BF_{10}=0.58; no group interaction) were not significant.

There were no significant correlations between the clinical trait variables (CIS-fatigue, SIP-total, SF-36 and disease duration) and neural outcome measures within the CFS group (all p>.05).

Functional connectivity

During feedback evaluation (70% trials), CFS patients showed reduced connectivity between SMA and the independently defined vACC-VOI compared to HC (xyz=-2,43,43, p_{fwe_VOI}=0.006). This effect was specific for 70% trials, being significantly stronger than during 30% trials (group by force interaction: xyz=-2,34,34, p_{fwe_VOI}=.023) within the same VOI(**Figure4H/I**). No relationships were observed with state-fatigue (CFS: r=-.017,p=.62, BF_{10}=0.14; HC: r=.26,p=.127, BF_{10}=0.60; no group interaction. No group differences were found for regions within the DLPFC clusters during feedback evaluation (70% trials).

During movement preparation, CFS patients showed reduced connectivity between SMA and sensorimotor cortex compared to HC (xyz = -32,-34,46, p_{fwe_VOI}=0.013). Higher levels of state fatigue were associated with stronger connectivity in both groups (CFS: r=.25, p=.020, BF_{10}=1.94; HC: r=.41, p=.029, BF_{10}=2.23), and this relationship was stronger for HC than for CFS patients (T_{112}=-2.55, p

=.012)**(Figure5D-F)**. Exploration over the whole brain did not reveal significant group differences in functional connectivity during feedback or preparation.

Discussion

This study investigated whether fatigue symptoms in CFS patients are linked to altered neuro-computational processes during monitoring and preparation of effortful physical activity. Patients and healthy controls had matched maximum voluntary contractions, produced comparable force levels during the task, and showed similar levels of muscular fatigue (i.e. change in MVC), yet CFS patients reported higher state-related fatigue, higher effort levels and stronger task-related increases in fatigue and pain of the right hand. There are two main novel findings. First, CFS patients showed an effort-dependent directional behavioural bias towards less effort investment, which was accompanied by reduced feedback-related activity in the DLPFC for the highest effort level. These effects were proportional to the patients' state-related fatigue, and to their prior beliefs about their ability to perform the task within the CFS group. Second, in an exploratory analysis, CFS patients showed higher preparation-related activity in the SMA, proportional to their state-related fatigue, and reduced connectivity between SMA and sensorimotor cortex during motor preparation, as compared to controls. These findings link fatigue symptoms to alterations in prefrontal and sensorimotor functioning, with the DLPFC being directly associated with prior beliefs about physical abilities and reduced effort investment, supporting and qualifying recent theoretical suggestions on neurocomputational mechanisms leading to the emergence and persistence of fatigue symptoms(22-24).

Cerebral and behavioural alterations during feedback processing

The feedback-related results extend previous reports on altered error-processing in vACC(15) and working-memory in DLPFC(10-12) of CFS patients, by showing that these regions are related to an effort-dependent and directional bias in error-related adjustments and higher perceived fatigue. Moreover, within CFS patients, behavioural bias and DLPFC activity were associated with lower performance expectations ("how much *will* you squeeze"), directly linking these prefrontal regions to prior beliefs of reduced physical abilities. Within the framework described in the introduction(22-24), these findings might reflect a prefrontal failure to evaluate fatigue and error signals, leaving patients' belief of being unable to successfully perform the task encapsulated from the actual consequences of their actions. Indeed, unlike HC, CFS patients stayed with their prior beliefs and failed to adjust their perceived performance assessed after the task ("How much *did* you squeeze") to feedback delivered during the task.

This interpretation is further supported by the observed reduced connectivity between SMA and ACC in CFS patients. The ACC is well connected to premotor regions and known to integrate interoceptive information and performance monitoring for decisions on post-error adjustments(47-49). In line with that, behavioural apathy has also been associated with reduced SMA-ACC connectivity(41). Clinically, this interpretation may also account for avoidance behaviours or reductions in physical/social activities commonly observed in CFS patients, by suggesting that high expected costs (i.e. fatigue) or low expected benefits (probability of reward or success) affect decisions to engage in these activities and that successful events do not contribute to a change in these expectations. It needs to be noted though that group differences on feedback related activity were more prominent in the DLPFC, while those on connectivity were more prominent within the vACC-VOI and that there was no significant relationship between these effects. Accordingly, it remains to be determined whether CFS-related alterations in DLPFC and vACC reflect the same process, or whether each region provides independent contributions to fatigue-related behaviours.

Fatigue-related alterations during motor preparation

During motor preparation, there was stronger SMA activity and reduced SMA-sensorimotor connectivity in CFS patients than in controls. The increase in SMA activity could not be driven by differences in preparing to produce different forces, since the two groups exerted overall matched forces during the task, and SMA activity did not scale with force delivered during the task. In fact, SMA activity in CFS patients was proportional to their state-related fatigue. These observations can be interpreted in the context of a recent qualification of the role of SMA in motor control, linking this motor region to the generation of predictions about the sensory consequences of actions(38, 39). In this framework, the level of SMA activity and its functional connectivity to sensorimotor regions observed in healthy controls would reflect neural computations of predictions that are relatively well-tuned to the actual somatosensory consequences of the forthcoming movement. By contrast, the observed increases in SMA activity and reductions in SMA-sensorimotor connectivity in CFS patients might reflect an enduring discrepancy between prior expectations and actual sensory evidence. Fatigue may then arise when sensory evidence is less than what was expected(50). By the same token, the increased preparation-related SMA activity found in CFS patients could reflect neural computations of exceedingly precise predictions of the somatosensory consequences of the forthcoming movement(22, 23), while the decreased SMA connectivity might reflect a systematic reduction of SMA sensitivity to the forthcoming somatosensory evidence, with a residual variation in connectivity still related to inter-

individual variation in fatigue perception. This interpretation fits with the observation that inhibition of SMA activity with transcranial magnetic stimulation leads to a reduction in effort perception(38). It needs to be noted that these results were based on an explorative analysis informed by a report that came out after publication of our pre-registration. Accordingly, replication in an independent sample is needed to confirm these results.

Conclusions

Clinical studies have highlighted the role of cognitive behavioural factors, such as dysfunctional beliefs on the persistence of fatigue in CFS. This study suggests that the DLPFC/ACC may play a role in the persistence of fatigue symptoms and behaviour in CFS patients, linking prior (meta-cognitive) beliefs about reduced physical abilities to reduced feedback-related activity in the DLPFC, and to reduced effort-investments in response to feedback. Additional exploratory analyses link fatigue symptoms in CFS patients to alterations in SMA activity and its connectivity with sensorimotor regions during movement preparation, suggesting a neural correlate for recent theoretical suggestions that fatigue may arise from increased precision of predicted sensory consequences of the upcoming action(22-24). This observation provides new ground for further investigation of the role of SMA in (psycho)somatic symptom perception, and for testing whether acute modulations of SMA activity (e.g. with non-invasive brain stimulation) could lead to changes in fatigue symptoms in CFS patients(38). Our results do not provide conclusion about whether SMA changes precede DLPFC changes, which could be tested in longitudinal studies following the transition from acute to chronic fatigue. Interpretation of (lack of) correlations between subjective reports and neural/behavioural measures within the HC group are limited because of its smaller sample size. Accordingly it remains to be tested in larger HC groups whether these relationships are specific to CFS patients or whether they reflect one end of a continuum. Finally, it remains to be seen whether changing dysfunctional beliefs, as achievable with cognitive behavioural therapy(28-30, 51-55), leads to corresponding changes in DLPFC/vACC activity and/or SMA connectivity during feedback processing. We are testing this hypothesis in an ongoing randomized controlled trial(36).

Figure legends

Figure 1: Task design. Participants are asked to prepare to produce one of three force levels (30%, 50% or 70% of their maximal voluntary contraction). After the presentation of a GO cue, participants flex their hand around a handgrip for about 1 second. After a short delay, participants are given feedback on the force produced on that trial (too much, correct, or too little). fMRI activity related to motor preparation was measured during the period between the onset of the instruction and the GO cues. fMRI activity related to feedback processing was measured at the onset of feedback.

Figure 2: Subjective and objective measures. A) CFS patients reported higher levels of state fatigue, before and after the task, than HC. **B and C)** Fatigue and Pain of the right hand, as measures with visual analogue scales, were higher and increased more after the task in CFS patients compared to HC. **D)** CFS patients reported higher effort levels than HC. **E)** (Change in) maximal voluntary contraction did not differ between CFS patients and HC before or after the task. **F)** Time courses of force production across trials per effort level, time locked to time of maximum exerted force. CFS patients exerted more force than HC on 30% trials, but showed no difference on 50% and 70% trials. MVC = maximal voluntary contraction. See **Table 3** for means and standard errors per group.

Figure 3: Behavioural results. A) Average force adjustments per effort level on trials following "Too much" and "Too little" feedback. Positive values indicate that the increase in force production following "too little" feedback is larger than the decrease following "too much" feedback. Negative values indicate that the increase in force production following "too little" feedback is smaller than the decrease following "too much" feedback. CFS patients show larger negative values with higher effort levels, while the opposite is seen for HC. **B)** Higher fatigue levels within CFS patients are associated with larger negative force adjustments on 70% trials (CFS: r=-0.26, p=0.015; HC: r=.038, p=.85; no group interaction) **C)** CFS patients that expect to produce insufficient force on 70% trials also show larger negative force adjustments on those trials (CFS: r=0.37, p<.001; HC: r=.28, p=.14; no group interaction).

Figure4. BOLD activity during feedback A) In the DLPFC, there was significantly decreased feedback-related activity during 70% trials in CFS patients compared to HC (in orange, cluster overlaid on a coronal view of a representative structural image, local maxima at -48, 14, 46, T = 4.39, $p_{fwecluster}$ = .006; and 24, 34, 44, T = 4.15, $p_{fwecluster}$ < .001). Results are shown at p<.05 fwe corrected at the cluster level, based on a whole brain threshold of p<0.001 uncorrected. **B)** Estimates of feedback-related activity extracted from the DLPFC clusters obtained for the 70% contrast. Note that this plot is presented for illustration purposes only because it is biased for a group difference on 70% trials. **C)** Estimates of feedback-related activity extracted from the independently defined VOI over the ventral anterior cingulate cortex (vACC) (8 mm sphere centred at -8,32,30, based on (15)). **D, E and F)** Relationship between DLPFC feedback-related activity and state fatigue (CFS: r = -.24, p = .024, HC r = .18, p = .34, no group interaction), force adjustments on 70% trials (CFS: r=0.26, p=0.016, HC r = .053, p = .79, no group interaction), and expected task performance for 70% trials (CFS: r = .24, p = .027, HC r = .15, p = .43, no group interaction). **H)** During feedback processing, there was significantly decreased connectivity between SMA and vACC in CFS patients compared to HC (in yellow, effect overlaid on a sagittal view of a representative structural image, local maximum at -2, 33, 33). The cluster was significant (p<.016 fwe peak-level corrected) within the vACC-VOI, (8 mm sphere centred at -8,32,30, based on (15)) . **I)** Difference in feedback-related SMA-vACC connectivity between CFS and HC as a function of force demand, extracted from the independently defined vACC-VOI (8 mm sphere centred at -8,32,30).

DLPFC = Dorsolateral prefrontal cortex, vACC = ventral anterior cingulated cortex, SMA = supplementary motor area.

Figure5. BOLD activity during motor preparation. A) In the SMA, there was significantly increased preparation-related activity in CFS patients compared to HC (in orange, cluster overlaid on a sagittal view of a representative structural image, local maximum at -4, -4, 68). The cluster was significant ($p<.05$ fwe peak-level corrected) within the apriori defined VOI (8 mm sphere centred around -5, -10, 67, based on (38)). For illustration purposes, results are shown at a threshold of $p<.001$ uncorrected. **B)** Estimates of preparation-related activity extracted from the a priori defined VOI ($F_{1,112}=4.77$, $p = .031$). **C)** Relationship between preparation—related activity and state fatigue (CFS: $r = .28$, $p = .009$, HC: $r = -.022$, $p = .91$, , no group interaction). **D)** During movement preparation, there was significantly decreased connectivity between SMA and sensorimotor cortex (SMC) in CFS patients compared to HC (in orange, cluster overlaid on a transverse view of a representative structural image, local maximum at -32, -34, 46). The cluster in the red circle was significant ($p<.05$ fwe peak-level corrected) within a VOI derived from an independent effect (movement execution) across both groups (local maximum at -30, -32, 50, radius = 8mm). Results are shown at a threshold of $p<.001$ uncorrected. **E)** Difference in preparation-related SMA-SMC connectivity between CFS and HC ($T_{1,112}=-2.45$, $p = .016$). **F)** Relationship between SMA-SMC connectivity and state fatigue (CFS: $r = .25$, $p = .020$, HC: $r = .41$, $p = .029$, group interaction: $T_{3,110}=-2,55$, $p =.012$). VOI = Volume of interest, SMC = sensorimotor cortex.

Tables

TABLE1: participant characteristics

		CFS			HC			
		Mean(SE)	range	N	Mean(SE)	range	N	T-value
Demographics	Age	33.9(1.2)	(18-60)	85	33.4(2)	(19-55)	29	.207 ns
	Education(0-7)	4.9(0.1)	(1-7)	85	4.9(0.2)	(4-7)	29	.236 ns
	Disease duration (years)	6.4(0.8)	(1-40)	85				
Functional status	CIS-fatigue (8-56)	51.5(0.5)	(40-56)	85	17.3(1.3)	(8-30)	29	31.53 **
	SIP-total (0-9937)	1667.1(57.6)	(719-2898)	85				
	SF-36 (0-100)	55.9(2.4)	(10-100)	85	94.5(2.4)	(40-100)	29	-8.84 **
	BDI (0-14)	3.6(0.3)	(0-11)	85	1.07(0.27)	(0-7)	29	4.66 **
Activity level	Mean Actometer score	66.2(2.1)	(25-125)	84	71.8(3.6)	(27-101)	26	-1.33 ns
Cognitive function	WAIS-dst (# correct)	60.2(1.2)	(30-86)	85	63.6(1.6)	(51-85)	29	- 1.501 ns
	Digit span total	12.7(0.3)	(7-20)	85	14.1(0.6)	(9-23)	29	- 2.176 *

*p<.05, **p<.001, ns = not significant

Table2:

Force level	"Too little"	"Correct"	"Too much"	"Too little"& "Too much"
CFS				
30%	5.15(0.38)	1.09(0.2)	-4.66(0.34)	0.49(0.41)
50%	6.62(0.44)	0.21(0.23)	-5.58(0.3)	1.05(0.39)
70%	6.4(0.45)	-0.54(0.24)	-7.27(0.49)	-0.87(0.43)*
HC				
30%	4.45(0.69)	1.72(0.36)	-5.35(0.52)	-0.9(0.76)
50%	5.87(0.64)	0.44(0.38)	-6.22(0.58)	-0.35(0.56)
70%	7.66(0.84)	-0.8(0.4)	-6.23(0.52)	1.42(0.76)

Means (standard error) of the adjustments made in exerted force following each feedback type. * differs from HC with p<.05

Table 3

	CFS		HC	
	Before	After	Before	After
State fatigue	41.03(2.07)**	59.52(2.41)**	5.2(1.67)	15.39(2.79)
Fatigue right hand	12.71(1.86)*	50.94(2.87)**	2.07(1.12)	26.55(3.8)
Pain right hand	6.82(1.4)*	35.18(2.99)**	1.55(1)	10.52(2.31)
Effort 30	27.8(2.49)	46.15(2.85)*	21.21(4.34)	27.76(5.55)
Effort 50	41.59(2.44)*	53.76(2.19)**	25.86(4.24)	37.07(5.02)
Effort 70	55.41(2.67)*	63.94(2.27)**	37.59(5.41)	37.24(5.28)
Expected performance (70%)	49.41(1.66)		51.55(2.85)	
Perceived performance (70%)		52.68(2.05)		53.28(2.65)
MVC	866.29(24.17)	911.66(28.99)	865.79(41.42)	956.9(41.4)
Mean force delivery 30%		37.47(0.92)*		33.45(33.45)
Mean force delivery 50%		48.6(1.04)		46.51(46.51)
Mean force delivery 70%		60.96(1.18)		62.97(62.97)

Means (standard error) of the subjective measures, force ability (MVC) and average force delivery across trials before and/or after task performance. MVC = maximal voluntary contraction. * differs from HC with p<.05. ** differs from HC with p<.001

Table4: fMRI results

BA	Region	Left/Right	xyz	k	T	cluster pfwe	peak pfwe
CFS<HC Incorrect>Correct 70%							
8	Middle frontal Gyrus	Left	-48,14,46	568	4.39	0.006	0.138
6	Middle frontal Gyrus	Left	-38,6,50		4.34		0.16
9	Middle frontal Gyrus	Left	-42,26,26		3.44		0.906
45	Inferior frontal Gyrus	Left	-38,-24,14	269	4.37	0.076	0.147
8	Superior frontal Gyrus	Right	24,34,44	1036	4.15	<.001	0.272
8	Superior frontal Gyrus	Right	34,10,52		4.01		0.384
44	Superior frontal Gyrus	Right	48,16,32		3.94		0.453
39	Lateral occipital cortex	Right	40,-60,30	278	3.91	0.069	0.476
39	Angular Gyrus	Right	56,-58,38		3.83		0.564
CFS>HC Incorrect>Correct 70%							
No suprathreshold voxels							
CFS>HC Instruction >rest[1]							
6	Supplementary motor cortex	left	-4,-4,68	4	3.21	0.015	0.017
CFS<HC Instruction >rest							
No suprathreshold voxels							

[1] p-values are corrected for the volume of interest (8 mm sphere centred at xyz = -5, -10, 67). No suprathreshold voxels were seen at the whole brain level. BA = Brodman area.

Acknowledgements and disclosures

This work was funded by a private foundation that wishes to stay anonymous. The identity of the foundation was disclosed to the editors and does not constitute, to the Journal's understanding, a conflict of interest. The funder had no role in the study design, data collection, data analysis, decision to publish, or preparation of the manuscript. All listed authors concur in submission and the final manuscript has been approved by all. Experimental procedures have been conducted in conformance with the policies and principles contained in the Federal Policy for the Protection of Human Subjects and in the Declaration of Helsinki. All authors report no biomedical financial interests or potential conflicts of interest.

We would like to thank our research assistant Iris Schmits for her help on recruitment and data collection.

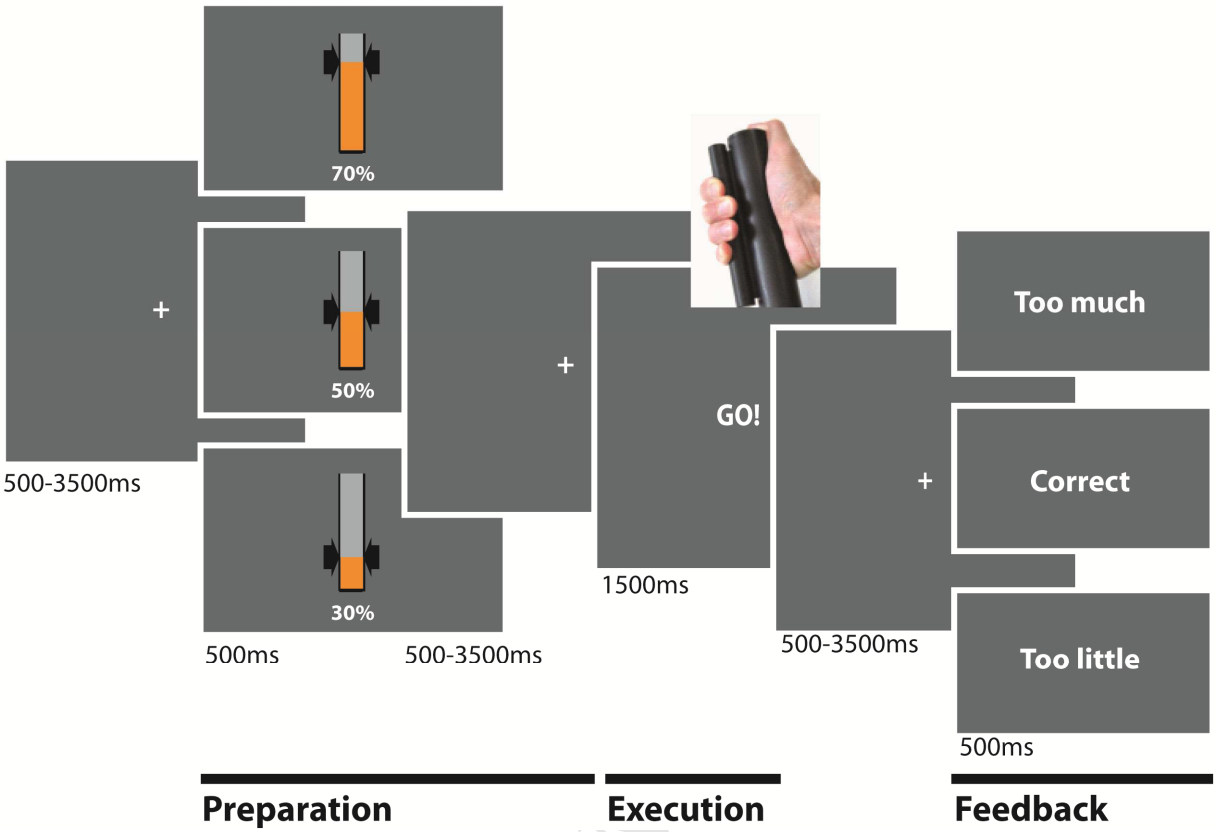
Literature

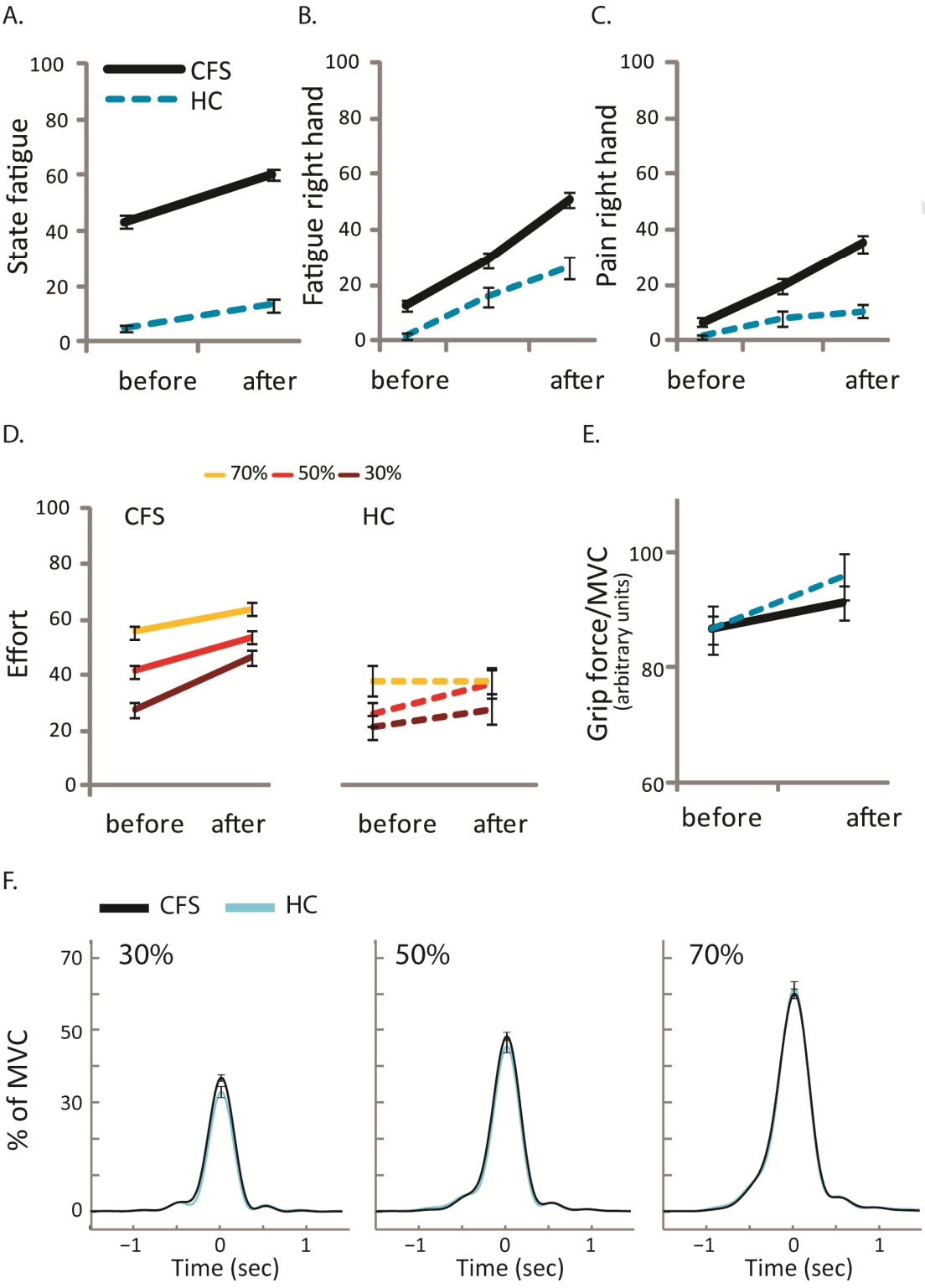
1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A (1994): The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of internal medicine*. 121:953-959.
2. Reeves WC, Lloyd A, Vernon SD (2003): Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Services Research*. 3:1-9.
3. Browning M, Fletcher P, Sharpe M (2011): Can neuroimaging help us to understand and classify somatoform disorders? A systematic and critical review. *Psychosomatic medicine*. 73:173-184.
4. de Lange F, Kalkman J, Bleijenberg G, Hagoort P, van der Meer J, Toni I (2005): Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage*. 26:777-781.
5. de Lange F, Koers A, Kalkman J, Bleijenberg G, Hagoort P, van der Meer J, et al. (2008): Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain*. 131:2172-2180.
6. van der Schaaf ME, Lange FP, Schmits IC, Geurts D, Roelofs K, van der Meer J, et al. (2016): Prefrontal structure varies as function of pain symptoms in patients with Chronic Fatigue Syndrome. *Biological psychiatry*.
7. Puri BK, Jakeman PM, Agour M, Gunatilake KD, Fernando KA, Gurusinghe AI, et al. (2012): Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study. *The British journal of radiology*. 85:3.
8. Shan ZY, Kwiatek R, Burnet R, Fante P, Staines DR, Marshall-Gradisnik SM, et al. (2016): Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study. *Journal of magnetic resonance imaging : JMRI*. 44:1301-1311.
9. Barnden LR, Crouch B, Kwiatek R, Burnet R, Del Fante P (2015): Evidence in chronic fatigue syndrome for severity-dependent upregulation of prefrontal myelination that is independent of anxiety and depression. *NMR in biomedicine*. 28:404-413.
10. Cook D, O'Connor P, Lange G, Steffener J (2007): Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. *NeuroImage*. 36:108-122.
11. Lange G, Steffener J, Cook D, Bly B, Christodoulou C, Liu WC, et al. (2005): Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory. *NeuroImage*. 26:513-524.
12. Caseras X, Mataix-Cols D, Giampietro V, Rimes K, Brammer M, Zelaya F, et al. (2006): Probing the working memory system in chronic fatigue syndrome: a functional magnetic resonance imaging study using the n-back task. *Psychosomatic medicine*. 68:947-955.
13. Mizuno K, Kawatani J, Tajima K, Sasaki AT, Yoneda T, Komi M, et al. (2016): Low putamen activity associated with poor reward sensitivity in childhood chronic fatigue syndrome. *NeuroImage: Clinical*. 12:600-606.
14. Miller AH, Jones JF, Drake DF, Tian H, Unger ER, Pagnoni G (2014): Decreased Basal Ganglia Activation in Subjects with Chronic Fatigue Syndrome: Association with Symptoms of Fatigue. *PloS one*. 9.
15. de Lange F, Kalkman J, Bleijenberg G, Hagoort P, van der Werf S, van der Meer J, et al. (2004): Neural correlates of the chronic fatigue syndrome--an fMRI study. *Brain*. 127:1948-1957.
16. Caseras X, Mataix-Cols D, Rimes K, Giampietro V, Brammer M, Zelaya F, et al. (2008): The neural correlates of fatigue: an exploratory imaginal fatigue provocation study in chronic fatigue syndrome. *Psychological medicine*. 38:941-951.

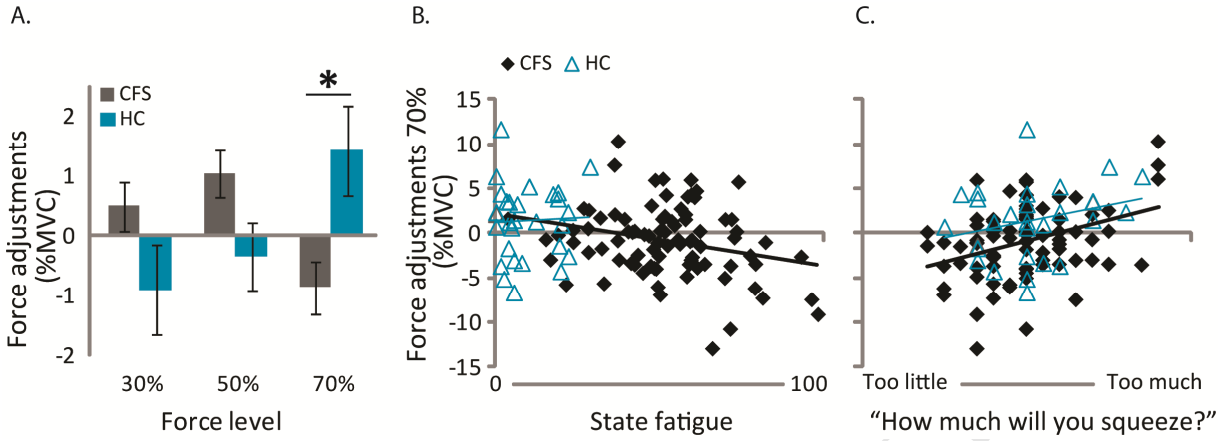
17. Werf SP, Prins JB, Vercoulen J, Meer JWM, Bleijenberg G (2000): Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. *Journal of psychosomatic research*. 49:373-379.
18. Nijs J, Aelbrecht S, Meeus M, Van Oosterwijck J, Zinzen E, Clarys P (2011): Tired of being inactive: a systematic literature review of physical activity, physiological exercise capacity and muscle strength in patients with chronic fatigue syndrome. *Disability and rehabilitation*. 33:1493-1500.
19. Schillings M, Kalkman J, van der Werf S, van Engelen B, Bleijenberg G, Zwarts M (2004): Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 115:2518-2524.
20. Riley M, O'Brien C, McCluskey D, Bell N, Nicholls D (1990): Aerobic work capacity in patients with chronic fatigue syndrome. *BMJ (Clinical research ed)*. 301:953-956.
21. Fry A, Martin M (1996): Fatigue in the chronic fatigue syndrome: a cognitive phenomenon? *Journal of psychosomatic research*. 41:415-426.
22. Edwards M, Adams R, Brown H, Pareés I, Friston K (2012): A Bayesian account of 'hysteria'. *Brain : a journal of neurology*. 135:3495-3512.
23. Stephan K, Manjaly Z, Mathys C, Weber L, Paliwal S, Gard T, et al. (2016): Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression. *Frontiers in human Neuroscience*. 10.
24. Petzschner FH, Weber LAE, Gard T, Stephan KE (2017): Computational Psychosomatics and Computational Psychiatry: Toward a Joint Framework for Differential Diagnosis. *Biol Psychiatry*. 82:421-430.
25. Brown RJ (2004): Psychological mechanisms of medically unexplained symptoms: an integrative conceptual model. *Psychological bulletin*. 130:793-812.
26. Knoop H, Prins J, Moss-Morris R, Bleijenberg G (2010): The central role of cognitive processes in the perpetuation of chronic fatigue syndrome. *Journal of psychosomatic research*. 68:489-494.
27. Vercoulen J, Swanink C, Galama J, Fennis J, Jongen P, Hommes O, et al. (1998): The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *Journal of psychosomatic research*. 45:507-517.
28. Heins MJ, Knoop H, Burk WJ, Bleijenberg G (2013): The process of cognitive behaviour therapy for chronic fatigue syndrome: which changes in perpetuating cognitions and behaviour are related to a reduction in fatigue? *Journal of psychosomatic research*. 75:235-241.
29. Wiborg J, Knoop H, Frank L, Bleijenberg G (2012): Towards an evidence-based treatment model for cognitive behavioral interventions focusing on chronic fatigue syndrome. *Journal of psychosomatic research*. 72:399-404.
30. Wiborg J, Knoop H, Prins J, Bleijenberg G (2011): Does a decrease in avoidance behavior and focusing on fatigue mediate the effect of cognitive behavior therapy for chronic fatigue syndrome? *Journal of psychosomatic research*. 70:306-310.
31. Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G (2010): How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychological medicine*. 40:1281-1287.
32. Heins M, Knoop H, Nijs J, Feskens R, Meeus M, Moorkens G, et al. (2012): Influence of Symptom Expectancies on Stair-Climbing Performance in Chronic Fatigue Syndrome: Effect of Study Context. *International journal of behavioral medicine*.
33. Nijs J, Meeus M, Heins M, Knoop H, Moorkens G, Bleijenberg G (2012): Kinesiophobia, catastrophizing and anticipated symptoms before stair climbing in chronic fatigue syndrome: an experimental study. *Disability and rehabilitation*. 34:1299-1305.

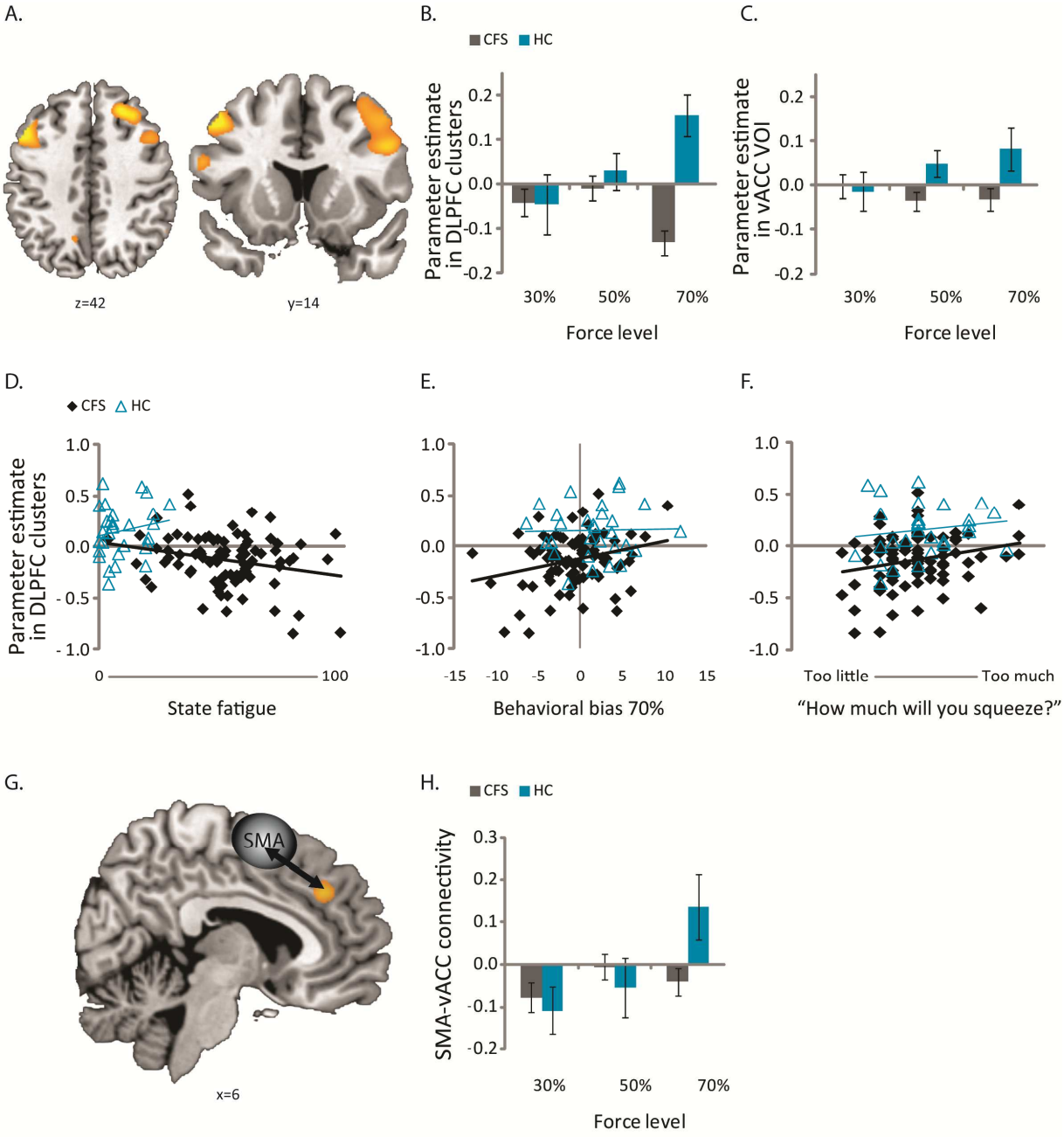
34. Deale A, Chalder T, Wessely S (1998): Illness beliefs and treatment outcome in chronic fatigue syndrome. *Journal of psychosomatic research*. 45:77-83.
35. Nijs J, Roussel N, Van Oosterwijck J, De Kooning M, Ickmans K, Struyf F, et al. (2013): Fear of movement and avoidance behaviour toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice. *Clinical rheumatology*. 32:1121-1129.
36. van Der Schaaf ME, Schmits IC, Roerink M, Geurts DE, Toni I, Roelofs K, et al. (2015): Investigating neural mechanisms of change of cognitive behavioural therapy for chronic fatigue syndrome: a randomized controlled trial. *BMC psychiatry*. 15:144.
37. Kuppuswamy A, Clark EV, Turner IF, Rothwell JC, Ward NS (2015): Post-stroke fatigue: a deficit in corticomotor excitability? *Brain : a journal of neurology*. 138:136-148.
38. Zénon A, Sidibé M, Olivier E (2015): Disrupting the supplementary motor area makes physical effort appear less effortful. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 35:8737-8744.
39. Haggard P, Whitford B (2004): Supplementary motor area provides an efferent signal for sensory suppression. *Brain research Cognitive brain research*. 19:52-58.
40. Klein-Flügge MC, Kennerley SW, Friston K, Bestmann S (2016): Neural Signatures of Value Comparison in Human Cingulate Cortex during Decisions Requiring an Effort-Reward Trade-off. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 36:10002-10015.
41. Bonnelle V, Manohar S, Behrens T, Husain M (2015): Individual Differences in Premotor Brain Systems Underlie Behavioral Apathy. *Cerebral cortex*
42. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A (1994): The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of internal medicine*. 121:953-959.
43. Vercoulen J, Swanink C, Fennis J, Galama J, van der Meer J, Bleijenberg G (1994): Dimensional assessment of chronic fatigue syndrome. *Journal of psychosomatic research*. 38:383-392.
44. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, et al. (2017): The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. *J Psychosom Res*. 98:40-46.
45. Bergner M, Bobbitt RA, Carter WB, Gilson BS (1981): The Sickness Impact Profile: development and final revision of a health status measure. *Medical care*. 19:787-805.
46. Eklund A, Nichols TE, Knutsson H (2016): Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences of the United States of America*. 113:7900-7905.
47. Boksem MAS, Ruys KI, Aarts H (2011): Facing disapproval: Performance monitoring in a social context. *Social Neuroscience*. 6:360-368.
48. Boksem MA, Meijman TF, Lorist MM (2006): Mental fatigue, motivation and action monitoring. *Biological psychology*. 72:123-132.
49. Critchley HD, Harrison NA (2013): Visceral influences on brain and behavior. *Neuron*. 77:624-638.
50. Kuppuswamy A, Rothwell J, Ward N (2015): A model of poststroke fatigue based on sensorimotor deficits. *Current opinion in neurology*. 28:582-586.
51. Knoop H, Bleijenberg G, Gielissen MF, van der Meer JW, White PD (2007): Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? *Psychotherapy and psychosomatics*. 76:171-176.
52. Knoop H, van der Meer JW, Bleijenberg G (2008): Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. *The British journal of psychiatry : the journal of mental science*. 193:340-341.

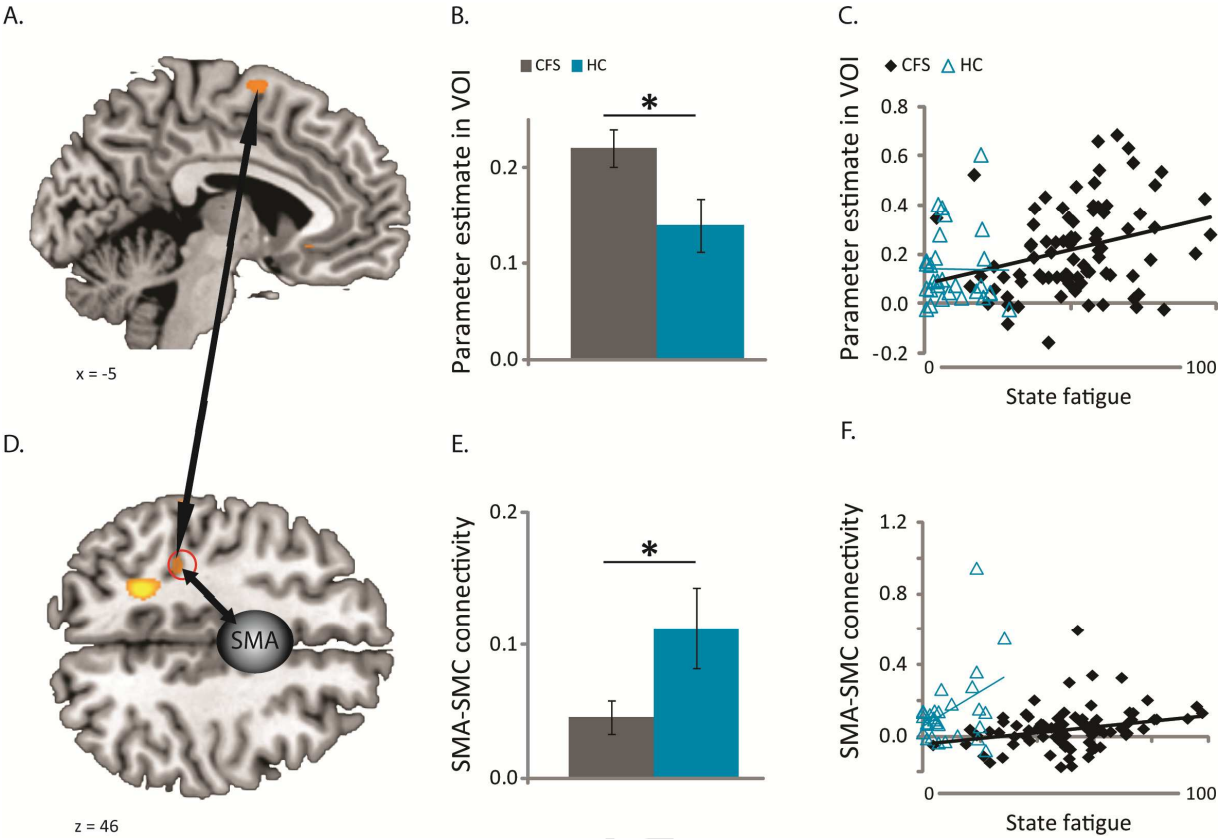
53. Tummers M, Knoop H, van Dam A, Bleijenberg G (2013): Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome. *Journal of psychosomatic research*. 74:373-377.
54. Wiborg JF, van Bussel J, van Dijk A, Bleijenberg G, Knoop H (2015): Randomised controlled trial of cognitive behaviour therapy delivered in groups of patients with chronic fatigue syndrome. *Psychotherapy and psychosomatics*. 84:368-376.
55. Prins J, Bleijenberg G, Bazelmans E, Elving L, de Boo T, Severens J, et al. (2001): Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet*. 357:841-847.




A.
B.
C.
CFS
HC
State fatigue
Fatigue right hand
Pain right hand
100
80
60
40
20
0
before
after
D.
E.
70%
50%
30%
CFS
HC
Effort
Grip force/MVC
(arbitrary units)
F.
30%
50%
70%
% of MVC
70
50
30
0
−1
0
1
Time (sec)




A.
z=42
y=14
B.
CFS HC
Parameter estimate in DLPFC clusters
0.2
0.1
0.0
-0.1
-0.2
30%
50%
70%
Force level
C.
Parameter estimate in vACC VOI
0.2
0.1
0.0
-0.1
-0.2
30%
50%
70%
Force level
D.
CFS HC
Parameter estimate in DLPFC clusters
1.0
0.5
0.0
- 0.5
- 1.0
0
100
State fatigue
E.
1.0
0.5
0.0
-0.5
-1.0
-15
-10
-5
0
5
10
15
Behavioral bias 70%
F.
1.0
0.5
0.0
-0.5
-1.0
Too little
Too much
"How much will you squeeze?"
G.
SMA
x=6
H.
CFS HC
SMA-vACC connectivity
0.3
0.2
0.1
0.0
-0.1
-0.2
30%
50%
70%
Force level



Fatigue Is Associated With Altered Monitoring and Preparation of Physical Effort in Patients With Chronic Fatigue Syndrome

Supplemental Information

Inclusion and exclusion criteria

Inclusion criteria for all participants were: female, between 18 and 65[1] years old, no use of psychotropic medication 6 months prior to testing, no current psychiatric disorder, except for specific phobias, as assessed with the Mini-International Neuropsychiatric Interview (MINI) (1), no severe obesity (BMI≤40), no contra-indication for MR-examinations, normal hearing and (corrected) vision, sufficient command of the Dutch language. Additional inclusion criteria for CFS patients were: meeting U.S. Centers for Disease Control (CDC) criteria for CFS including severe fatigue lasting longer than 6 months and at least 4 out of 8 additional symptoms (post-exertional malaise, unrefreshing sleep, memory and concentration problems, muscle pain, joint pain, headaches, tender lymph nodes and sore throat) (2, 3), a score of 40 or higher on the subscale fatigue severity of the checklist individual strength (CIS-fatigue) (4), and a score of 700 or higher on the Sickness Impact Profile 8 (SIP8 total) (5) assessing the level of functional disability. Physicians of the department of internal medicine evaluated the medical records of referred patients. When the physicians deemed the patients not sufficiently examined, they were seen for history, full physical examination, case history evaluation and laboratory tests following the National CFS guideline, as used at the department of internal medicine, in accordance with the guidelines of the CDC (3, 6). Additional inclusion criteria for healthy controls were a score lower than 35 on the CIS- fatigue subscale and no chronic medical condition, including no chronic pain (See (7)).

[1] The initial maximal age of 55 reported in van der Schaaf et al. (7) was extended to 65 due to low number of eligible patients.

Methods

MVC calibration and practice session

Prior to the MRI session the task was practiced, including written and oral instruction and MVC calibration. MVC was calibrated before and after the task to assess (change in) physical ability. This practice session was performed in a dummy scanner, to ensure identical body posture. Subjects were presented with a moving red bar on the screen representing the force exerted on the handgrip. They were instructed and verbally encouraged to squeeze as hard as they could. This was repeated 5 times and the maximal value was used for their MVC. Practice consisted of 1 block of each force level until the force delivered in 4 trials in a row was within the correct window (force level ± 8%). Valid visual feedback was presented in the form of the words "Too little", "Correct" and "Too much", as well as a vertical scale indicating the force delivered and a marker indicating the desired force. Note that during the main experiment only the words were presented. Directly prior to the main task in the MRI scanner subjects were again presented with 3 trials of each force level.

Task procedure

To provide online feedback during the experiment, the raw output of the handgrip device was recalculated as the proportion of MVC (0-100%) by dividing the difference between maximal exerted force during the force-production epoch and raw baseline output at the start of the trial.

In the "GO" trials (44 trials for each of the three force levels), feedback was delivered according to the following scheme. A running average over the last ten trials of each force level was used to define a window (mean ± 1.6*SD; in the first 10 trials the mean was replaced by the instructed force level and the SD was set to 5). If the force delivered by the participant on that trial was outside this window, the feedback consisted of the labels "Too much" or "Too little", as applicable. If the force delivered was within the window, the feedback was random, distributed between "Correct" (60% of trials), "Too

much" (20% of trials) and "Too little" (20% of trials). This method ensured that feedback occurrences were similar across participants and groups and that each participant received on average 44% "Correct", 25% "Too much" and 31% "Too little" feedback. See **Table S1** and supplementary analysis for an overview and statistics on feedback occurrences.

Design estimability

The parameters of the experimental design (e.g. instructed delay between instruction and execution, proportion of no-go trials) were chosen on the basis of simulations of different multiple regression models. Those simulations were implemented in order to satisfy multiple conflicting demands, e.g. 1) minimize BOLD-related correlations between preparation and execution regressors; 2) gather a substantial number of trials to robustly estimate preparation and feedback-related effects; 3) keep the scanning window within a time-frame that would not compromise participants compliance with the task. The simulations guided us to the parameters used in this study, predicting correlations between preparation and execution regressors of ~35%. Previous studies using this approach have shown that this level of collinearity, given the strength of preparation-related effects, is suitable to isolate statistically robust effects (e.g. (8, 9) and that the corresponding effects are estimable. Corr(SPM.xX.X) was used to compute the correlations between the preparation and execution regressors. The mean absolute correlation coefficients between the three preparation regressors and the motor execution regressor were 0.126, 0.057 and 0.068 for 30%, 50% and 70%, respectively. The mean absolute correlation coefficients between the three preparation regressors and the force-magnitude regressor were 0.333, 0.066 and 0.377 for 30%, 50% and 70%, respectively

Pre-processing of gripforce data

Exerted force was measured continuously (60Hz) during the task with a MR-compatible handgrip device (Current Designs, Inc). Continuous grip-force measurements were low-pass filtered (2.5 Hz), split into trials, referenced to zero at each trial onset, and normalized to MVC (MATLAB 2012b). Force delivery onset was defined by a combination of force exceeding 5% of MVC and rate of force change higher than 0.6% per sample. The end of the force delivery period was defined as the point in time when exerted force was reduced back to 5% or below. Duration was calculated as the difference between onset and endof force delivery. Force delivery not occurring between the onset of the "GO" and feedback signals was considered incorrect.

Neuroimaging data: Scan parameters

Functional MRI was assessed using a multi echo, T2*-weighted, gradient-echo planar imaging (EPI) sequence (TR = 2190 ms, TE = 9.0/19.28/29.56/39.84 ms, flip angle = 90°, 36 axial slices aligned with AC-PC plane, slice matrix size = 64 x 64, slice thickness = 3.0 mm, slice gap = 0.3 mm, FOV = 212*212 mm). Anatomical images were obtained before functional imaging for spatial normalization purposes using a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR\TE: 2300\3.03 ms, flip angle = 8°, 192 sagittal slices, FoV: 256x256 mm, voxel size: 1 mm^3, slice thickness: 1 mm).

Neuroimaging data: Pre-processing

Images were pre-processed and analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London) and FSL (FMRIB's Software Library, Version 6.00, www.fmrib.ox.ac.uk/fsl). Images were first checked for spike-artefacts and realigned to the first volume using data from the shortest TE. After realignment, TE's were combined into a single dataset using a weighted summation of the four TEs

(10). 30 multi echo scans acquired prior to the start of the experiment were used to calculate contrast-to-noise ratio maps for each TE. These maps were then used to calculate an optimal voxel-wise weighting between the four echoes using in-house software, maximizing the contribution of each echo according to its contrast-to-noise ratio.

FSL was used to remove motion artifacts using data-driven Independent Component Analysis-based strategy for Automatic Removal of Motion Artefacts (ICA-AROMA) (11). Realigned and combined images were first registered to high resolution structural and/or standard space images using FLIRT in FSL (12). Registration from high resolution structural to standard space was then further refined using FNIRT nonlinear registration in FSL. Images were minimally smoothed with an isotropic Gaussian kernel of 5mm full width at half maximum. Probabilistic ICA was achieved using Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC, part of the FMRIB Software Library (FSL)), with automatic estimation of the number of independent components. Next, IC components were identified as motion-related artefacts based on its high-frequency content, correlation with realignment parameters obtained from the first realignment step, edge fraction, and CSF fraction. An IC was classified as motion-related when it exceeded at least one of three criteria: 1) exceeding a decision boundary combining the edge fraction and maximum RP correlation, 2) a CSF fraction > 10%, or 3) a high-frequency content > 35% (non-aggressive denoising) (11). ICs identified as motion artefacts were removed from the fMRI data and de-noised data was smoothed with an isotropic Gaussian kernel of 8mm full-width at half-maximum for further statistical analysis.

Neuroimaging data: First level General Linear Model

8 nuisance regressors were included to the model. 6 head movement parameters obtained from the realignment procedure and two parameters to model global intensity changes (the time series of the white matter and cerebral spinal fluid (13). Instruction and feedback events during which the subjects

incorrectly squeezed were excluded from these regressors and instead included in the force production regressor.

Neuroimaging data: Main task effects

Main effects and group differences were assessed with two sample T-tests on the beta images of the first level contrasts of interest. Main task effects across groups were explored to describe general activity patterns induced by the task for the following four contrasts. 1) Instruction versus rest, 2) squeeze parameter, 3) correct versus incorrect, 4) incorrect versus correct. All main task effects are reported with a statistical threshold of $p<.05$ family wise error (fwe) corrected at the whole brain level.

Results

Subject exclusions

Two patients were excluded due to excessive head movement (>3mm). Five patients were excluded due to incorrect task performance in more than 30% of trials, i.e. no force delivery (2 patients) or force delivery outside the predefined 'GO' window. One patient was excluded because her behavioural adjustments were outside the range of the group (>4 SD). One patient and one healthy control were excluded due to technical failure of online force measurements. See Figure S1 for a flowchart of subject recruitment.

Number of feedback trials

A repeated measures ANOVA with the factors force (3 levels), feedback (3 levels) and group (CFS, HC) was done to check if the feedback occurrences were the same between groups. This analysis revealed no group difference on feedback occurrence (all $p >.5$). Similarly, there was no group difference on the occurrence of invalid feedback (all $p >.5$). Across both groups, there was a significant

force*feedback interaction ($F_{3,110}$ = 43.7, p<.001). For 30% and 50%, participants received more often "Too much" than "Too little" (T_{113} = -15.07, p<.001, T_{113} = -9.54, p<.001,) while for 70%, participants received more often "Too little" than "Too much" ((T_{113} = 4.10, p<.001). Concerning the validity of the trials, there was a significant force * feedback interaction (F = 18.16, p <.001). For 30%, the proportion invalid "Too little" was higher than the proportion invalid "Too much" (T_{113} = 4.09, p <.001), while for 50 and 70% the proportion invalid "Too much" was higher than the proportion invalid "Too little" (T_{113} = -1.99, p = .049, T_{113} = -4.75, p <.001). These results do not have any consequences for the interpretation of group effects as effects were the same in both groups.

To assess whether individual differences in feedback occurrences explained the observed reductions in DLPFC activity for high-effort trials, we assessed the relationship between DLPFC activity and feedback occurrences. DLPFC activity (70%) was not correlated with the proportion "correct" (CFS: r=.176, p=.107; HC: r = .109, p =.574) nor with the difference between the proportion "too little" and the proportion "too much" (CFS: r=-.187, p=.087; HC: r=-.197, p =.306) on 70% trials.

Effects of intervening trials

Behavioural adjustments were calculated as the change in force level between two trials of the same force level. However, since trial-types were randomized, trials of the same trial-type did not always directly follow each other and intervening trials may have affected behavioural adjustments. To rule out potential effects of intervening trials, several supplementary analyses were conducted.

First distance between trials of the same type were calculated and compared between groups. In both groups, about 30% of adjustments were calculated on directly preceding trials and the majority of adjustments (>75%) were calculated on trails with a maximal distance of 4 trials. There was no difference between groups on the average distance in trials (p >.05 for all effort levels).

Second, it was assessed whether there was a difference between groups in the contribution of feedback given on trials that had larger trial distances. This was done to test the possibility that CFS patients and controls may differ in how well they remembered feedback of trials, when there were intervening trials of a different type. To this end, a general linear model was built per subject assessing the effect of feedback on behavioural adjustments on a trial by trial basis. Behavioural adjustment (relative to the previous trial of the same type) was included as dependent variable and two feedback variables were included as predictor variables (too little = 1, correct = 0 too much = -1). One feedback variable included the given feedback on directly preceding trials (fb1), the second feedback variable included the given feedback on trials that had one or more intervening trials of a different type (fb>1). Both predictors contributed significantly to behavioural adjustments (CFS fb1: beta = 7.58, T = 16.6 p <.001; CFS fb>1: beta = 5.02, T = 20.59 p <.001; HC fb1: beta = 8.56, T= 14.14. p <.001, HC fb>1: beta = 4.59, T= 15.06, p <.001) and this contribution was not different between groups (fb1: T = -1.13, p = .25, fb>1: T = .937, p = .35). Taken together, these results suggest that intervening trials did not differently affect behavioural adjustments between CFS patients and HC.

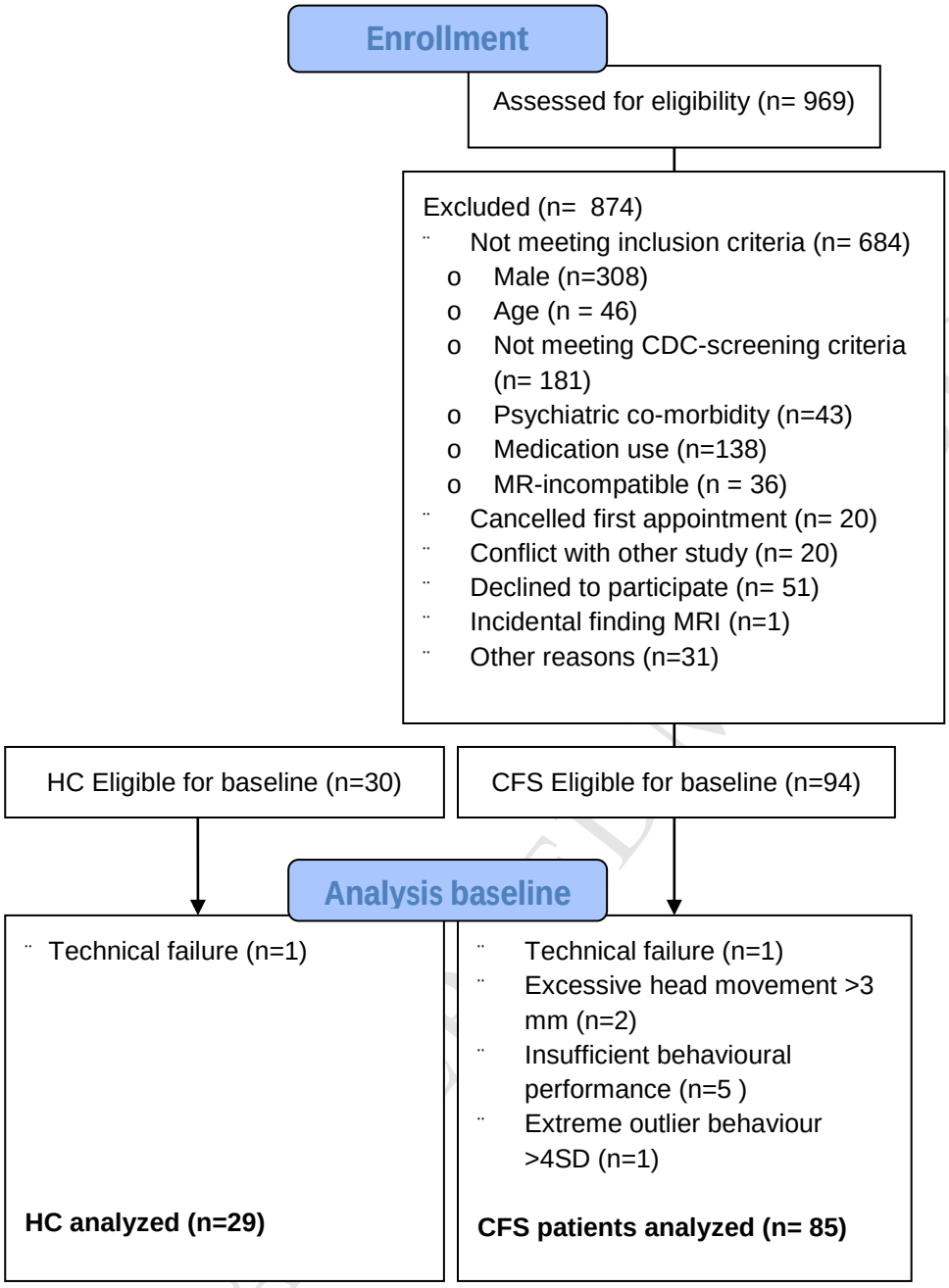


Figure S1: Flowchart

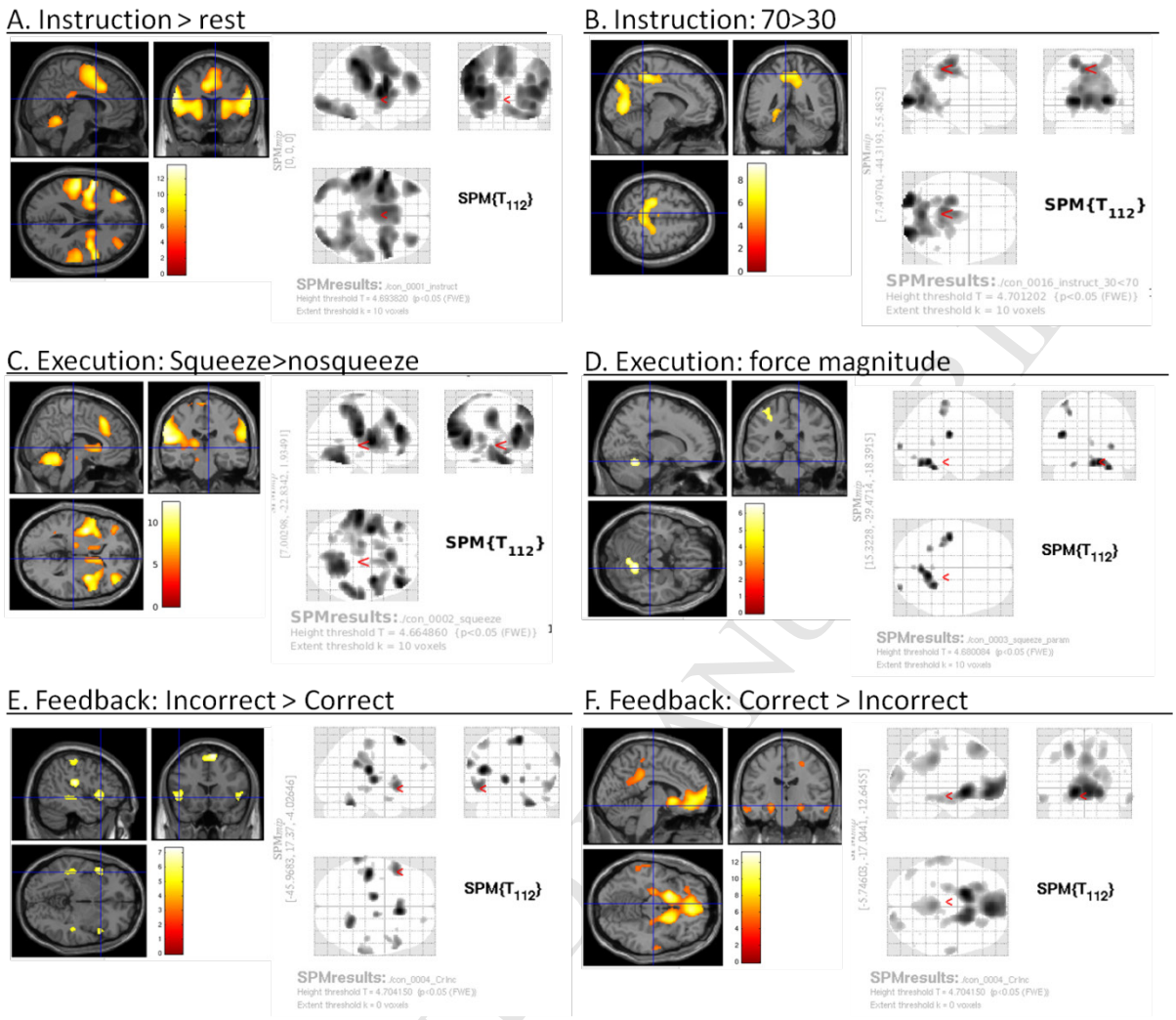
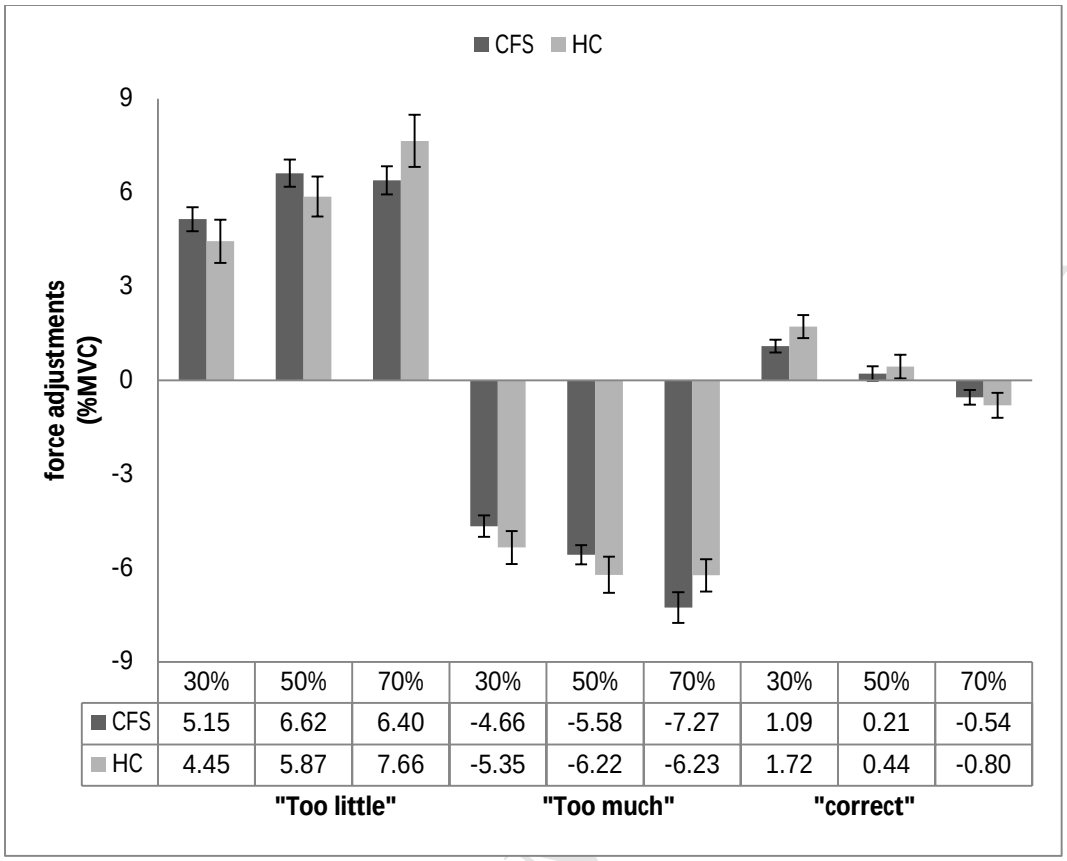


Figure S2. Main task effects. Main effects across the CFS and control group during A) instruction all versus rest, B) instruction 70% vs 30%, C) motor execution and D) its parametric modulation by the force magnitude of the squeeze event, E and F) feedback processing. Significant results are shown on a MNI-template and with glass brains with a statistical threshold of p<.05 fwe corrected at the whole brain. See Tables S2-S6 for all positive and negative effects.



	30%	50%	70%	30%	50%	70%	30%	50%	70%
CFS	5.15	6.62	6.40	-4.66	-5.58	-7.27	1.09	0.21	-0.54
HC	4.45	5.87	7.66	-5.35	-6.22	-6.23	1.72	0.44	-0.80

Figure S3. Behavioural adjustments presented separately for each feedback type.

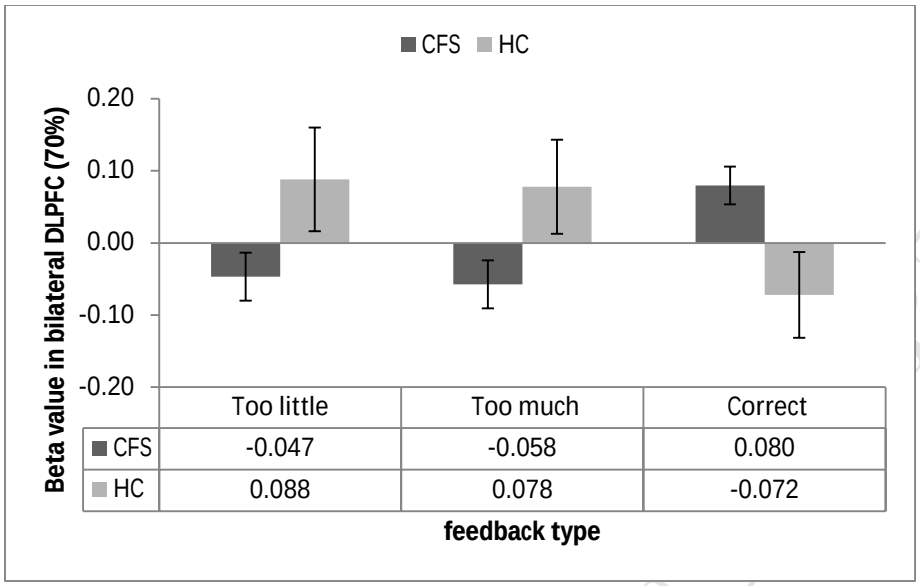


Figure S4. Estimates of feedback-related activity on 70% trials presented for each feedback type separately. Data is extracted from the DLPFC clusters obtained for the incorrect versus correct contrast on 70% trials.

Tables:

Table S1: Number of trials per force level and feedback

		given feedback: nr of trials (% of total)			Invalid feedback: nr of trials (% of that type)	
Group	Instruction	"Too little"	"Correct"	"Too much"	"Too Little"	"Too much"
CFS	30	9 (21%)	19 (43%)	16 (36%)	3 (31%)	3 (22%)
	50	11 (26%)	19 (43%)	13 (36%)	3 (26%)	4 (31%)
	70	13 (31%)	19 (44%)	11 (25%)	3 (23%)	4 (37%)
	Total	34 (26%)	57 (43%)	40 (31%)	9 (26%)	11 (29%)
HC	30	9 (21%)	18 (42%)	16 (37%)	3 (33%)	4 (25%)
	50	11 (26%)	19 (42%)	13 (37%)	3 (28%)	4 (31%)
	70	13 (29%)	20 (46%)	11 (25%)	3 (27%)	4 (34%)
	Total	33 (25%)	58 (44%)	40 (31%)	10 (30%)	12 (30%)

Table S2: fMRI Main effect: Instruction>Rest

BA	Region		xyz	k	T	cluster pfwe	peak pfwe
Positive							
40	Supramarginal gyrus (posterior)	Left	-50,-40,52	16827	13.66	<.001	<.001
13	Insular cortex (middle)	Left	-36,-4,10		13.65		<.001
44	Precentral gyrus	Left	-54,4,16		13.32		<.001
6	Central opercular cortex	Right	46,4,10	3444	11.91	<.001	<.001
44/6	Precentral gyrus	Right	58,8,22		11.46		<.001
49	Putamen	Right	22,4,10		9.64		<.001
19	Lateral occipital cortex (inferior)	Right	40,-82,-10	2717	11.01	<.001	<.001
	Cerebellum	Right	36,-52,-26		10.56		<.001
18	Occipital pole	Right	30,-92,-6		9.53		<.001
9/10	Frontal pole	Left	-38,44,28	993	10.92	<.001	<.001
19	Lateral occipital cortex (inferior)	Left	-40,-88,-8	1754	10.73	<.001	<.001
37	Temporal occipital fusiform cortex	Left	-38,-50,-22		9.20		<.001
9/10	Frontal pole	Right	38,44,30	648	9.98	<.001	<.001
1	Post central gyrus	Right	60,-18,40	3023	9.09	<.001	<.001
40	Supramarginal gyrus (anterior)	Right	54,-32,52		8.80		<.001
40	Postcentral gyrus	Right	58,-20,22		8.55		<.001
	Cingulate gyrus		0,-30,26	204	6.94	<.001	<.001
Negative							
18	Visual association cortex	Right	22,-72,-6	14281	11.57	<.001	<.001
19	Lateral occipital cortex (superior)	Left	-26,-82,22		11.24		<.001
18	Visual association cortex		0,-84,-10		11.17		<.001
9	Superior frontal gyrus	Left	-6,50,24	5821	10.85	<.001	<.001
10	Paracingulate gyrus	Right	6,52,18		10.03		<.001
8	Superior frontal gyrus	Right	8,30,60		7.49		<.001
5	Inferior frontal gyrus	Left	-54,24,10	2441	9.75	<.001	<.001
47	Frontal orbital cortex	Left	-46,26,-10		8.89		<.001
47	Frontal orbital cortex	Left	-32,18,-16		8.85		<.001
13	Insular cortex (anterior)	Right	28,20,-16	1091	8.96	<.001	<.001
9	Inferior frontal gyrus	Right	56,28,12		8.57		<.001
47	Frontal orbital cortex	Right	48,30,-8		7.67		<.001
	Cerebellum	Left	-14,-48,38	1143	8.05	<.001	<.001
31	Precuneus	Right	10,-50,38		6.60		<.001
6	Middle frontal gyrus	Left	-40,12,50	576	7.62	<.001	<.001
8	Middle frontal gyrus	Left	-26,26,42		5.47		0.003
21	Middle temporal gyrus (posterior)	Right	56,-16,-12	319	6.96	<.001	<.001
21	Middle temporal gyrus (posterior)	Right	50,-12,-20		5.65		<.001
7	Superior parietal lobule	Right	26,-56,56	119	6.89	<.001	<.001
WM		Left	-26,-24,30	14	4.92	0.015	0.023

Table S3: Main effect instruction 70>30

BA	Region		xyz	k	T	cluster pfwe	peak pfwe
Positive							
17	Primary visual cortex	Right	24,-96,6	8385	9.41	<.001	<.001
18	Visual association cortex	Left	-24,-92,4		9.21		<.001
17	Primary visual cortex	Left	-2,-74,6		8.18		<.001
4	Post central gyrus	Left	-24,-28,60	3059	7.64	<.001	<.001
31	Cingulate gyrus (middle)	Left	-10,-38,50		7.50		<.001
31	Cingulate gyrus (middle)	Left	-4,-24,48		7.06		<.001
WM		Right	46,-48,2	33	5.19	0.005	0.009
Negative							
6	Precentral gyrus	Left	-56,4,36	1277	7.40	<.001	<.001
40	Superior parietal lobule	Left	-42,-40,46		7.32		<.001
1	Post central gyrus	Left	-56,-20,32		5.77		<.001
18	Occipital fusiform gyrus		20,-90,-14	139	7.03	<.001	<.001
18	Occipital fusiform gyrus	Left	-24,-88,-14	87	6.33	0.001	<.001

Table S4: Main effect squeeze > nosqueeze

BA	Region		xyz	k	T	cluster pfwe	peak pfwe
Positive							
48	Caudate	Left	-38,-2,4	7060	12.45	<.001	<.001
1	Post central gyrus	Left	-58,-20,16		12.39		<.001
40	Supramarginal gyrus (anterior)	Left	-62,-22,28		11.74		<.001
22	Middle frontal gyrus	Right	44,42,20	1330	12.15	<.001	<.001
47	Orbital frontal cortex	Right	24,44,-12		8.72		<.001
13	Insula (anterior)	Right	38,2,6	2688	11.95	<.001	<.001
44	Rolandic operculum	Right	54,8,6		9.10		<.001
13	Insula	Right	36,16,2		8.15		<.001
	Cerebellum	Right	16,-48,-24	2118	11.13	<.001	<.001
	Cerebellum	Right	20,-56,-24		10.89		<.001
	Cerebellum	Right	6,-64,-20		9.40		<.001
8	Cingulate gyrus (middle)	Right	2,26,38	1429	10.87	<.001	<.001
40	Inferior parietal cortex	Right	48,-42,56	1695	10.36	<.001	<.001
40	Supramarginal gyrus	Right	58,-30,50		10.26		<.001
40	Supramarginal gyrus	Right	62,-18,24		9.92		<.001
46	Inferior frontal gyrus	Left	-42,40,16	576	10.10	<.001	<.001
48	Caudate	Left	-10,12,-2	307	7.24	<.001	<.001
	Cerebellum	Left	-24,-66,-24	70	7.11	0.002	<.001
	Cerebellum	Left	-24,-58,-26		6.22		<.001
37	Fusiform	Left	-22,42,-12	17	6.24	0.014	<.001
NA	Precuneus	Left	-34,-52,4	44	6.11	0.004	<.001
	Brainstem	Left	-12,-22,-18	39	5.26	0.005	0.006
	Brainstem	Right	8,-16,-14	13	5.22	0.017	0.007
Negative							
39	Angular gyrus	Right	58,-54,20	35118	16.73	<.001	<.001
31	Precuneus	Right	2,-50,40		14.37		<.001
39	Angular gyrus	Left	-46,-60,22		14.36		<.001
10	Frontal Pole	Right	2,58,-14	6358	11.74	<.001	<.001
11	Paracingulate gyrus	Right	4,34,-10		11.63		<.001
10	Paracingulate gyrus	Right	8,50,4		9.16		<.001
9	Middle frontal gyrus	Left	-26,34,40	2673	10.36	<.001	<.001
6	Middle frontal gyrus	Left	-36,4,52		10.09		<.001
8	Middle frontal gyrus	Left	-32,24,50		9.98		<.001
45	Inferior frontal gyrus	Right	56,28,10	292	8.80	<.001	<.001
47	Frontal orbital cortex	Right	42,32,-12		7.14		<.001
47	Inferior frontal gyrus	Right	50,30,-6		6.47		<.001
6	Precentral gyrus	Right	38,-4,46	546	6.45	<.001	<.001
54	Hippocampus	Right	24,-8,-18	61	6.18	0.002	<.001
9	Middle frontal gyrus	Right	36,16,26	121	5.58	<.001	0.002
6	Superior frontal gyrus	Right	12,-2,66	117	5.27	<.001	0.006
6	Superior frontal gyrus	Right	18,4,70		5.19		0.008
6	Supplementary motor area	Left	-10,8,52	18	4.99	0.013	0.016

Table S5: Main effect squeeze parameter

BA	Region		xyz	k	T	cluster pfwe	peak pfwe
Positive							
1	Central opercular cortex	Left	-40,-22,20	135	6.57	<.001	<.001
	Cerebellum 45	Right	14,-52,-18	490	6.48	<.001	<.001
	Vermis 6	Right	4,-62,-20		6.37		<.001
	Cerebellum 6	Right	26,-44,-28		6.27		<.001
18	Occipital pole	Right	32,-94,4	45	5.70	0.004	0.001
4	Post central gyrus	Left	-30,-32,50	208	5.68	<.001	0.001
5	Post central gyrus	Left	-36,-28,64		5.61		0.002
	Cerebellum 6	Left	-24,-50,-22	51	5.53	0.003	0.002
	Lingual gyrus	Right	2,-74,-12	19	5.13	0.012	0.01
	Vermis 45	Right	2,-46,8	31	5.04	0.007	0.014
Negative							
6	Precentral gyrus	Right	10,-26,60	327	6.50	<.001	<.001
1	Precentral gyrus	Left	-10,-32,64		5.50		0.002
13	Insular cortex (anterior)	Left	-28,24,-2	218	6.30	<.001	<.001
6	Precentral gyrus	Right	50,0,34	2788	6.11	<.001	<.001
9	Middle frontal gyrus	Right	50,36,22		6.11		<.001
13	Insular cortex (anterior)	Right	32,26,0		6.11		<.001
8	Superior frontal gyrus	Right	6,20,56	446	6.04	<.001	<.001
8	Superior frontal gyrus	Right	6,28,48		5.64		0.001
6	Precentral gyrus	Left	-48,-6,36	112	5.36	<.001	0.004
18	Occipital fusiform gyrus	Right	20,-90,-10	33	5.10	0.006	0.011
40	Angular gyrus	Right	48,-44,36	95	4.98	0.001	0.017
40	Supramarginal gyrus (posterior)	Right	50,-38,42		4.94		0.02
6	Precentral gyrus	Left	-40,-4,48	17	4.87	0.013	0.026
44	Central opercular cortex	Left	-56,12,14	11	4.83	0.019	0.029

Table S6: Main effect Incorrect>Correct

BA	Region		xyz	k	T	cluster pfwe	peak pfwe
Positive							
1	Parietal operculum cortex	Left	-44,-24,22	366	7.34	<.001	<.001
6	Superior frontal gyrus	Right	8,20,62	352	7.27	<.001	<.001
50	Thalamus	Left	-12,-18,8	170	6.95	<.001	<.001
	Cerebellum 6	Right	22,-50,-24	265	6.61	<.001	<.001
39	Supramarginal gyrus (posterior)	Left	-64,-42,30	153	6.34	<.001	<.001
44	Inferior frontal gyrus (pars opercularis)	Left	-48,14,0	398	6.25	<.001	<.001
50	Thalamus	Right	14,-14,8	69	5.94	0.001	<.001
44	Inferior frontal gyrus (pars opercularis)	Right	54,18,0	221	5.80	<.001	0.001
44	Inferior frontal gyrus (pars opercularis)	Right	60,12,10		5.55		0.002
40	Supramarginal gyrus (posterior)	Right	64,-36,40	253	5.70	<.001	0.001
1	Postcentral gyrus	Left	-42,-26,58	218	5.60	<.001	0.002
22	Superior temporal gyrus (anterior)	Right	48,4,-18	38	5.28	0.004	0.006
23	Middle temporal gyrus (posterior)	Right	46,-28,-4	37	5.26	0.005	0.007
21	Middle temporal gyrus (posterior)	Left	-48,-30,-4	90	5.12	0.001	0.011
9/10	Frontal Pole	Right	22,54,26	32	5.10	0.006	0.012
1	Postcentral gyrus	Left	-54,-18,40	27	4.87	0.007	0.028
Negative							
48/4							
9	Putamen	Left	-16,8,-8	6648	13.22	<.001	<.001
10/1							
1	Paracingulate gyrus	Right	4,44,-8		11.92		<.001
48/4							
9	Putamen	Right	16,12,-8		11.27		<.001
23	Cingulate gyrus (posterior)		0,-36,36	1976	8.36	<.001	<.001
5	Precentral gyrus	Right	4,-32,54		6.08		<.001
8	Frontal eye fields	Left	-24,28,54	680	8.34	<.001	<.001
18	V2	Right	16,-96,16	631	7.29	<.001	<.001
18	V2	Right	28,-84,12		6.43		<.001
18	V2	Right	28,-96,-4		5.44		0.003
21	Middle temporal gyrus	Left	-64,-26,-18	310	6.98	<.001	<.001
37	Fusiform gyrus	Left	-60,-40,-16		6.46		<.001
21	Middle temporal gyrus	Right	64,-12,-20	171	6.71	<.001	<.001
8	Frontal eye fields	Right	26,36,50	233	6.42	<.001	<.001
39	Angular gyrus	Left	-44,-72,40	127	5.72	<.001	0.001
6	Precentral gyrus	Right	24,-20,54	101	5.59	<.001	0.002
37	Left fusiform	Left	-30,-38,-18	35	5.24	0.005	0.007

Table S7. Summary of all reported correlations and their Bayes factor per paragraph

		CFS			HC			Interaction
		r	p	BF10	r	p	BF10	
Subjective reports								
state-fatigue	Effort (all)	0.106	0.334	0.021	0.442	0.016	**3.59**	T=-2.42*
Force adjustments								
Adjustment bias (70%)	State-fatigue	-0.26	0.015	**2.51**	0.038	0.85	0.24	No
	Performance expectations	0.37	<.001	**45.3**	0.28	0.14	0.65	No
Beliefs about performance abilities								
Perceived performance	Performance expectations	0.24	0.029	**1.43**	0.26	-0.172	0.56	No
	Actual feedback received	0.146	0.185	0.32	0.478	0.009	**6.12**	No
Neuroimaging								
feedback in DLPFC (70%)	State-fatigue	-0.24	0.024	**1.63**	0.19	0.34	0.36	No
	Adjustment bias (70%)	0.26	0.016	**2.33**	0.026	0.89	0.23	No
	Performance expectations	-0.24	0.27	**1.51**	0.15	0.43	0.31	No
feedback in vACC (70%)	State-fatigue	0.062	0.57	0.16	0.038	0.84	0.24	No
	Adjustment bias (70%)	0.039	0.72	0.14	0.056	0.77	0.24	No
	Performance expectations	0.019	0.86	0.16	0.26	0.17	0.56	No
Preparation in SMA (all)	State-fatigue	0.28	0.009	**4.01**	-0.022	0.91	0.23	No
	Effort (all)	-0.11	0.34	0.21	0.13	0.5	0.29	No
	Performance expectations	0.01	0.95	0.22	-0.017	0.38	0.58	No
Functional Connectivity								
SMA-vACC	State-fatigue	-0.017	0.62	0.14	0.26	0.127	0.6	No
SMA-S1M1	State-fatigue	0.25	0.2	**1.94**	0.41	0.029	**2.23**	T=-2.55*

* p<.05

Supplemental References

1. Sheehan D, Lecrubier Y, Sheehan K, Amorim P, Janavs J, Weiller E, et al. (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry*. 59 Suppl 20:22.
2. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A (1994): The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of internal medicine*. 121:953-959.
3. Reeves WC, Lloyd A, Vernon SD (2003): Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Services Research*. 3:1-9.
4. Vercoulen J, Swanink C, Fennis J, Galama J, van der Meer J, Bleijenberg G (1994): Dimensional assessment of chronic fatigue syndrome. *Journal of psychosomatic research*. 38:383-392.
5. Bergner M, Bobbitt RA, Carter WB, Gilson BS (1981): The Sickness Impact Profile: development and final revision of a health status measure. *Medical care*. 19:787-805.
6. Prins, Elving, Koning, Bleijenberg, Meer vd (2013): Richtlijn Diagnose, behandeling, begeleiding en beoordeling van patiënten met het chronisch vermoeidheidssyndroom (CVS). Nijmegen: Kwaliteitsinstituut voor de Gezondheidszorg.
7. van Der Schaaf ME, Schmits IC, Roerink M, Geurts DE, Toni I, Roelofs K, et al. (2015): Investigating neural mechanisms of change of cognitive behavioural therapy for chronic fatigue syndrome: a randomized controlled trial. *BMC psychiatry*. 15:144.
8. Thoenissen D, Zilles K, Toni I (2002): Differential involvement of parietal and precentral regions in movement preparation and motor intention. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 22:9024-9034.
9. Beurze SM, Toni I, Pisella L, Medendorp WP (2010): Reference frames for reach planning in human parietofrontal cortex. *J Neurophysiol*. 104:1736-1745.
10. Poser BA, Versluis MJ, Hoogduin JM, Norris DG (2006): BOLD contrast sensitivity enhancement and artifact reduction with multiecho EPI: Parallel-acquired inhomogeneity-desensitized fMRI. *Magnetic resonance in medicine*. 55:1227-1235.
11. Pruim R, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF (2015): ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage*. 112:267-277.
12. Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*. 17:825-841.
13. Verhagen L, Dijkerman H, Grol M, Toni I (2008): Perceptuo-motor interactions during prehension movements. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 28:4726-4761.