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Disentangling pain and fatigue in chronic fatigue syndrome: a resting state connectivity study before and after cognitive behavioral therapy

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Abstract

Background. Fatigue is a central feature of myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), but many ME/CFS patients also report comorbid pain symptoms. It remains unclear whether these symptoms are related to similar or dissociable brain networks. This study used resting-state fMRI to disentangle networks associated with fatigue and pain symptoms in ME/CFS patients, and to link changes in those networks to clinical improvements following cognitive behavioral therapy (CBT).

Methods. Relationships between pain and fatigue symptoms and cortico-cortical connectivity were assessed within ME/CFS patients at baseline ($N = 72$) and after CBT ($N = 33$) and waiting list (WL, $N = 18$) and compared to healthy controls (HC, $N = 29$). The analyses focused on four networks previously associated with pain and/or fatigue, i.e. the fronto-parietal network (FPN), premotor network (PMN), somatomotor network (SMN), and default mode network (DMN).

Results. At baseline, variation in pain and fatigue symptoms related to partially dissociable brain networks. Fatigue was associated with higher SMN-PMN connectivity and lower SMN-DMN connectivity. Pain was associated with lower PMN-DMN connectivity. CBT improved SMN-DMN connectivity, compared to WL. Larger clinical improvements were associated with larger increases in frontal SMN-DMN connectivity. No CBT effects were observed for PMN-DMN or SMN-PMN connectivity.

Conclusions. These results provide insight into the dissociable neural mechanisms underlying fatigue and pain symptoms in ME/CFS and how they are affected by CBT in successfully treated patients. Further investigation of how and in whom behavioral and biomedical treatments affect these networks is warranted to improve and individualize existing or new treatments for ME/CFS.

Introduction

Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) is characterized by extreme fatigue that significantly interferes with social, professional, and daily life activities. Besides disabling fatigue symptoms, ME/CFS patients often experience high comorbidity of pain disorders and hyperalgesia, such as fibromyalgia or irritable bowel syndrome (Aaron et al., 2001; Buchwald, Pearlman, Kith, Katon, & Schmaling, 1997; Castro-Marrero et al., 2017; Krupp, Jandorp, Coyle, & Mendelson, 1993; Surian & Baraniuk, 2020). Current treatments are often aimed at either fatigue or pain, while it is not given that treating one symptom will also resolve the other. However, the high comorbidity of fatigue and pain, as well as the similarities in their subjective, self-reported, and multidimensional character, make it hard to provide empirical arguments to guide treatment toward one or another. At the brain level, fatigue and pain both involve sensory, affective, and cognitive processes that are supported by distributed and overlapping neural circuits (Apkarian, Bushnell, Treede, & Zubieta, 2005; Buchel, Geuter, Sprenger, & Eippert, 2014; Davis, 2000; Maksoud et al., 2020; Muller & Apps, 2019; Song et al., 2021; Stephan et al., 2016). It might be possible to leverage those neural circuits to better differentiate these symptoms experienced by ME/CFS patients. Accordingly, the current study used resting-state functional magnetic resonance imaging (fMRI) to disentangle the neural networks associated with pain and fatigue symptoms in ME/CFS patients and test whether and how they are affected by cognitive behavioral therapy (CBT) for ME/CFS. The

results of this study may provide new insights into the symptom specific neural pathology of pain and fatigue, to ultimately better target and individualize both medical and behavioral treatments in ME/CFS.

Previous studies have used resting-state fMRI to investigate the neural network characteristics of either fatigue symptoms (for a systematic review, see Maksoud et al. (2020)) or pain symptoms (for a systematic review see Apkarian et al. (2005)). Using various methodological approaches (e.g. seed-based connectivity, principal component network analysis, graph theory), both fields indicate remarkable overlapping involvement of sensory, motor, prefrontal and fronto-parietal networks. Specifically, two studies that compared seed-based connectivity between ME/CFS patients and healthy controls (HC) report altered connectivity between the precuneus (=posterior default mode network [DMN]) and clusters in the primary motor area (precentral-gyrus), supplementary motor area (SMA), and prefrontal cortex (superior and medial frontal gyrus and anterior cingulate) which scaled with fatigue severity (Boissoneault et al., 2016; Kim et al., 2015a). Additionally, Gay et al. (2016) reported altered connectivity between the nodes of the frontoparietal network (FPN) and between the sensorimotor network (SMN) and cingulate cortex in ME/CFS compared to HC. Similarly, studies comparing chronic pain populations with HC, report differences in connectivity of sensorimotor network (i.e. SMN), supplementary motor cortex, anterior and posterior cingulate, insula, and amygdala (Apkarian et al., 2005; Baliki, Mansour, Baria, & Apkarian, 2014; Buchel et al., 2014; Farmer, Baliki, & Apkarian, 2012; Pfannmoller & Lotze, 2019; Sandstrom et al., 2022; Song et al., 2021). Moreover, a review of longitudinal studies by (Pfannmoller & Lotze, 2019) suggests that alterations in particularly DMN and FPN connectivity are involved in the chronification of pain conditions.

However, these studies did not directly compare pain and fatigue conditions or symptoms, or took into account its comorbidity. Accordingly, the question remains whether these networks play specific or common roles in fatigue or pain. So far, only a few studies did compare pain and fatigue-related connectivity patterns within one patient population. Specifically, using graph theoretical measures a recent study assessed symptom-specific associations in patients with ankylosing spondylitis and showed a partial network-level dissociation between fatigue- and pain-related brain connectivity (Liu et al., 2020). While functional connectivity of the DMN nodes with the rest of the brain was associated with both pain and fatigue, connectivity of the pre-central gyrus (part of the SMN) and superior parietal gyrus were only associated with fatigue. In line with this, two other studies in ME/CFS patients revealed that functional connectivity between the sensorimotor cortex and the SMA during preparation of effortful exertions was associated with fatigue (van der Schaaf et al., 2018), while structural integrity of the dorsolateral-prefrontal cortex was associated with pain and not fatigue symptoms (van der Schaaf et al., 2017). Together, this suggest that networks involving sensory-motor regions may play a specific role in fatigue symptoms, networks involving dorsolateral prefrontal cortex may play specific role in pain symptoms and that the DMN may be involved in both pain and fatigue symptoms.

Here we build on these findings and use resting state connectivity in ME/CFS patients to test the hypothesis that fatigue and pain involve partly dissociable patterns of neural connectivity, focusing on four networks that have previously been associated with fatigue or pain: the FPN, (related to pain [van der Schaaf et al., 2017]); the SMN and the premotor/supplementary motor network (PMN) (related to fatigue [van der Schaaf et al., 2018]), and the DMN (the most commonly reported network to be involved in both fatigue (ME/CFS) and pain (fibromyalgia) conditions (Fallon, Chiu, Nurmikko, & Stancak, 2016; Kim et al., 2015a, 2015b; Kong et al., 2013; Maksoud et al., 2020; Shan et al., 2018, 2020). To investigate this hypothesis, we first performed a network-based analysis, using the four major networks described above, to assess relationships between pain or fatigue symptoms and within and between network connectivity within the ME/CFS group, followed by post-hoc seed-based analyses to anatomically qualify the network-based results. More specifically, we hypothesize that pain symptoms are associated with connectivity of the FPN, fatigue symptoms are associated with connectivity of the SMN and PMN and both symptoms are associated with connectivity of the DMN.

CBT for ME/CFS aims to reduce fatigue by improving the sleep-wake cycle, regulation, gradual increase of (physical) activities and changing fatigue-related cognitions and behaviors in 12–14 individual sessions over a period of 6 months with a trained cognitive behavioral therapist. It has shown to successfully reduce fatigue and pain in a substantial subgroup of treated patients (Knoop, Bleijenberg, Gielissen, van der Meer, & White, 2007; Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008). However, it remains unclear what neurobiological mechanisms may underlie these clinical improvements and whether they involve general or domain specific networks. Accordingly, we tested whether symptom improvements in pain and fatigue after CBT (compared to waiting list and healthy controls) were associated with changes in neural connectivity. We hypothesize that CBT-induced improvements in pain are associated with changes in FPN connectivity while improvements in fatigue are associated with changes in SMN and/or PMN connectivity. Results of this study will provide insight into the neural mechanisms underlying fatigue and pain symptoms and whether or not these mechanisms are modulated by CBT.

Methods

Participants

Ninety-four female ME/CFS patients, between 18 and 65 years old, that met U.S. Centers for Disease Control (CDC)-criteria for ME/CFS (revised in 2003) (Fukuda et al., 1994; Reeves, Lloyd, & Vernon, 2003) and scored ⩾40 on the subscale fatigue of the checklist individual strength (CIS-fatigue) (Vercoulen et al., 1994; Worm-Smeitink et al., 2017), and ⩾700 on the Sickness Impact Profile-8 (SIP8total) (Bergner, Bobbitt, Carter, & Gilson, 1981) and thirty gender, age and education-matched healthy controls (HC)(<35 on CIS-fatigue, and no chronic medical condition) were included. For a complete list of in- and exclusion criteria see Supplement.

Procedure, randomization and intervention

Patients were informed about the study by their treating psychologists at the Expert Centre of Chronic Fatigue in Nijmegen, The Netherlands. Eligible patients were invited for a first baseline assessment (T0), after which they were randomly assigned to CBT ($n = 59$) or waiting list (WL; $n = 29$) by supporting staff who were not directly involved in the study. Six eligible patients declined from randomization but were included in the baseline

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analysis. Six months after CBT/WL, patients were invited for the second assessment (T1). HC were recruited through advertisements and flyers. Eligible HC were also tested twice with 6 months in between, to control for test-retest effects.

CBT consisted of 12–14 individual sessions within ~6 months with a trained cognitive behavioral therapist and took place at the Expert Centre of Chronic Fatigue (ECCF) in Nijmegen, The Netherlands. CBT included goal setting, regulation of the sleep-wake cycle, regulation/grading of physical activities while challenging fatigue-related cognitions and behaviors, realization of the prior set goals, reappraisal of fatigue and relapse prevention (van Der Schaaf et al., 2015). Patients that were assigned to WL did not receive any treatment or control intervention and started CBT after the second assessment.

Clinical data

For clinical characterization fatigue severity (CIS-fatigue [Vercoulen et al., 1994; Worm-Smeitink et al., 2017]), daily functioning (SIP-total [only in ME/CFS] [Bergner et al., 1981]), depressive symptoms (Beck depression inventory primary care [BDI-PC]), disease duration, age and education level (Verhage, 1964) were assessed. Successful treatment was defined by a clinically significant improvement on fatigue severity, i.e. scoring lower than 35 and a reliable change index of >1.96 on the CIS-fatigue, as defined in our preregistration (van Der Schaaf et al., 2015).

To assess relationships with fatigue and pain, two retrospective and two momentary outcome measures were selected. Selection of the retrospective measures was based on its common use in the literature. Selection of the momentary measures was based on previous results that demonstrated significant associations with neural activity and neuroanatomy.

1) Fatigue severity over the past two weeks (CIS-fatigue) (Vercoulen et al., 1994; Worm-Smeitink et al., 2017). This measure is commonly used in fatigue populations, and measures retrospective self-reported fatigue over the past 2 weeks. It includes a cut-off score for severely fatigued ME/CFS patients, which was used for patient selection in this study (see above).
2) Pain-related disability (pain subscale of the RAND-36 [RAND-pain] [Aaronson et al., 1998]). This measure is commonly used in pain populations and asks retrospectively about how much pain someone experienced in the past 4 weeks, and how much the pain interfered with daily activities.
3) Fatigue across the testing day (average of 3 measurements of the subscale fatigue of the profile of moods scale questionnaires (POMS-fatigue) (McNair, Lorr, & Doppleman, 1971; Shacham, 1983). This measure was associated with neural activity in van der Schaaf et al. (2018). It has additional value over the CIS-fatigue as it was not used for patient selection, and it provides an overall level of fatigue during the testing day.
4) Pain-occurrence (diary scores). Participants indicated the presence (yes or no) of muscle pain, joint pain, and/or headaches on four time points of the day during 12 consecutive days. Presence of pain was calculated as the average percentage of all time points with pain. This measure associated with neuroanatomy of the DLPFC in van der Schaaf et al. (2017). It has additional value over the RAND-pain as it provides a more direct measure of the occurrence of pain symptoms based on momentary assessments, rather than retrospective measurements.

Neuroimaging data collection

A 5-min resting-state scan was assessed, using a multi echo T2*-weighted, gradient-echo planar imaging (EPI) sequence (TR = 2000 ms, TE = 9.0/19.28/29.56/39.84 ms, flip angle = 90°, voxel size = 3.3 × 3.3 × 3.3 mm, slice thickness: 3.0 mm, 150 scans). During the scan, the room was dark and subjects were asked to lie still with their eyes open to avoid falling asleep. The resting-state scan was assessed at the end of a larger imaging protocol of which the results are published elsewhere (van der Schaaf et al., 2017; van der Schaaf et al., 2018). Resting-state was preceded by approximately 1.5 h of functional and anatomical imaging and a 15 min break after the first 45 min (see [van Der Schaaf et al., 2015]). Anatomical images were obtained at the start of the protocol, 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: 256 × 256 mm, voxel size: 1 mm^3, slice thickness: 1 mm).

Statistical analysis

Clinical characterization of the patient population

Clinical and demographic data were compared between the ME/CFS and HC groups at baseline using two sample *t* tests (except for education, which was analyzed with a Mann–Whitney-*U* test) in SPSS (version 27). Clinical changes were compared between CBT and WL (including all participants who completed the study), using repeated measures ANOVA with time (T0, T1) as a within-subjects factor and randomization (CBT, WL) as between-subjects factors, and with age and education as covariates of no interest. A p value of <0.05 was considered significant. Pearson correlation between clinical outcome variables is reported to test for multicollinearity, which is relevant for interpreting the specificity of brain-symptoms relationships for either pain or fatigue.

Neuroimaging analysis

Images were pre-processed and analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London), FSL (FMRIB's Software Library, Version 5.0.9, www.fmrib.ox.ac.uk/fsl) and in-house matlab codes (see online Supplement). A network-based analysis, using four major networks (see below), was done to compare ME/CFS and HC at baseline, and to assess relationships between connectivity and the clinical measures within the ME/CFS group. This was followed by a comparison of changes in network-connectivity between CBT, WL and HC groups, and its relationships with clinical change within the CBT group. Post-hoc seed-based analyses were used to investigate the robustness of the network-based results and to examine the anatomical specificity of the effects. If the network-level effects can also be observed in the seed-level analysis, this shows that they are robust to the exact ROI definition. It also allowed us to investigate if specific components of each network were driving the observed associations.

The network analysis was based on the MIST atlas (Urchs et al., 2017) (https://simexp.github.io/multiscale_dashboard/index.html). The hierarchical structure of this atlas allows for investigation of the data at different resolutions, and its independence from the test data avoids biases given differences in the groups size. We considered four networks derived from previous work showing the involvement of regions within those networks in ME/CFS: (1) the fronto-parietal task control network (FPN,

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corresponding to the DLPFC seed-region reported in [van der Schaaf et al., 2017]; 8 regions at the s36 level). (2) the somatomotor network (SMN, corresponding to the S1M1 seed-region reported in (van der Schaaf et al., 2018), 7 regions at the s7 level). (3) the premotor and supplementary motor network (PMN, corresponding to the SMA seed-region reported in (van der Schaaf et al., 2018), 4 regions at the s36 level) and (4) the default mode network (DMN, 22 regions). The latter was included because the DMN is one of the most reported networks of which connectivity with other brain regions is altered in both fatigue and pain conditions (Fallon et al., 2016; Kim et al., 2015a, 2015b; Kong et al., 2013; Maksoud et al., 2020; Shan et al., 2018, 2020). fMRI signals were extracted from 41 regions (online Supplementary Table S1 and Fig. 1a). We implemented post-hoc connectivity analyses on the three seed-regions identified by our previous work (van der Schaaf et al., 2017; van der Schaaf et al., 2018), defined as 8 mm spheres located in (1) the dorsolateral prefrontal gyrus (DLPFC; xyz = −342 631), (2) the supplementary motor area (PMN-seed; xyz = **−5**,−10,67) and (3) the somatomotor region (SMN-seed; xyz = −30,−32,50).

A general linear model (GLM) was applied on the time courses of each voxel within each network-region or seed (Geerligs, Cam, & Campbell, 2018; Geerligs, Tsvetanov, Cam, & Henson, 2017) and included 32 confound and noise regressors including six head-motion parameters, their first-order temporal, squares and squared derivatives, and average signals in the WM and CSF (Satterthwaite et al., 2013). Data and model regressors were band-pass filtered (0.008–0.1 Hz), by including a discrete cosine transform set in the GLM, ensuring that nuisance regression and filtering were performed simultaneously. Data were pre-whitened by inverting an autocorrelation model (Friston et al., 2002). (see online Supplement).

For the network-analysis, Pearson's correlation between all 41 regions was estimated from the whitened residuals of first level model (Geerligs, Cam, & Henson, 2016). The correlation matrices were Fisher z-transformed and reduced by averaging the values across all regions within the four major networks. This resulted in a correlation matrix with 4 within and 6 between network correlations (10 in total). These correlation matrices were compared between groups using regression analysis in matlab. Differences in network connectivity between the ME/CFS and HC groups were assessed at baseline/T0. To assess treatment effects on network connectivity, difference-matrices were calculated (T1−T0) and compared between CBT and WL and HC groups. To assess relationships between network-connectivity and (changes in) fatigue and pain, regression analyses were done within the ME/CFS group for each clinical variable separately (i.e. CIS-fatigue, POMS-fatigue, RAND-pain and pain occurrence). When significant, it was tested whether the relationship remained significant when including all four clinical variables into the model. p values were adjusted by false discovery rate (FDR), correcting for 10 comparisons and considered significant when <0.05.

When the network analysis revealed significant results, seed-based connectivity of the corresponding seed was assessed for the same contrast/relationship. For this, contrasts capturing cerebral activity associated with the seeds time series were taken to the second level in SPM. Statistical inferences for these analyses are based on cluster-level statistics familywise error (FWE) correction for multiple comparisons, with cluster-forming threshold of p = 0.001 [$p_{wb\_cluster}$], either at the whole brain ($p_{wb\_fwe\_cluster}$) or, when whole brain analysis was not significant, small-volume corrected for the voxels within the network with which where associations were shown in the network-level analysis ($p_{sv\_fwe\_cluster}$). Beta-values were extracted from significant clusters for

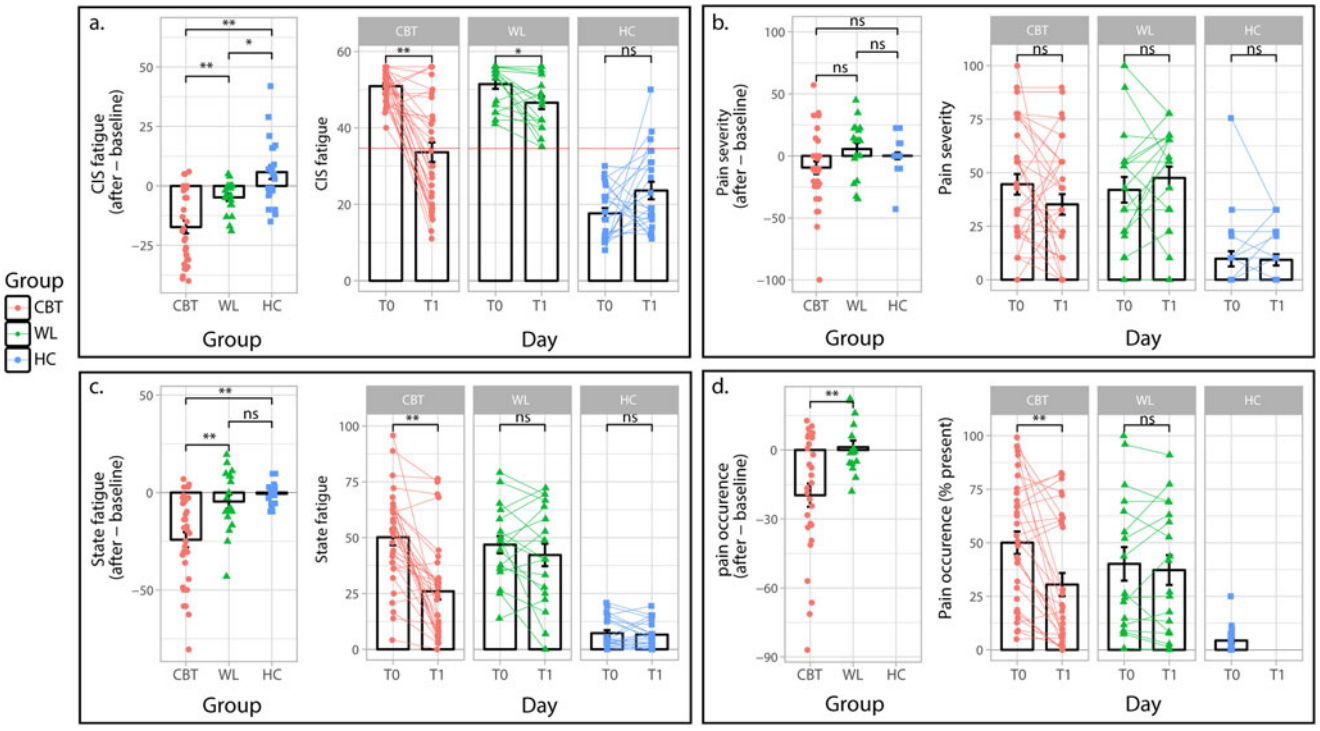

Figure 1. Clinical outcome measures. Change between T1 and baseline (left) and score per day for (a) CIS fatigue, (b) Pain severity as measured with the RAND-36, (c) Fatigue across the testing day as measured with the POMS-fatigue and (d) pain occurrence as measured with diary-scores. CIS, Checklist Individual Strength; POMS, Profile of Moods State; ns, not significant, * = p < 0.05, ** = p < 0.001.

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visualization and post-hoc group comparisons and to assess relationships with (change in) fatigue and pain. Exploratory seed-based analysis of remaining seeds is reported in the online Supplement. For all second-level analyses age and education were included as covariates of no interest.

Results

Participants

Resting-state data was not collected in all participants. See the study flowchart in the online Supplement for excluded and missing data. Baseline resting state scans were available for 72 ME/CFS patients and 29 controls. Follow-up resting state scans were available of 51 ME/CFS patients (33 CBT, 18 WL) and 25 controls. Diary-scores and BDI were missing for 8 participants (See Tables 1 and 2) but this did not affect the N for our main analysis.

Clinical outcome measures

ME/CFS patients and HC were matched on sex (all female), age, and education (all $p > 0.05$). Following inclusion criteria, ME/CFS patients scored higher than HC on the CIS-fatigue questionnaire. Patients with ME/CFS also reported higher POMS-fatigue, higher pain-occurrence, higher RAND-pain, and more depressive symptoms (Table 1).

CBT significantly reduced all clinical symptoms compared to WL (all $p < 0.05$) except for depressive symptoms and RAND-pain (Table 2). Out of the 33 patients that received CBT and completed both test days, 18 (55%) were successfully treated according to our predefined criteria (van Der Schaaf et al., 2015). The CBT and WL groups did not differ on age, education, disease duration or time between assessments. For HC no significant changes were observed on CIS-fatigue ($T_{21} = -5.818$, $p = 0.062$), POMS-fatigue ($T_{23} = 0.597$, $p = 0.555$), RAND-pain ($T_{21} = 0.0350$, $p = 0.972$) or BDI ($T_{21} = 1.250$, $p = 0.225$).

Pearson correlations within the CBT group revealed that CIS-fatigue and POMS-fatigue were not correlated on T0 ($N = 72$, $r = 0.145$, $p = 0.224$). Pain-occurrence and RAND-pain were significantly correlated on T0 ($N = 67$, $r = -0.643$, $p = <0.001$). There were also correlations between CIS-fatigue and pain-occurrence ($r = 0.24$, $p = 0.048$) and between POMS-fatigue and RAND-pain($r = 0.28$, $p = 0.018$). The change in CIS-fatigue, POMS-fatigue, RAND-pain and Pain occurrence between T1 and T0 were all significantly correlated ($p < 0.03$, all r between 0.27 and 0.69).

Baseline

No significant group differences were observed between the connectivity matrices of ME/CFS patients and HC at baseline (Fig. 2a, Table 3). However, regression analysis within the ME/CFS group revealed significant correlations between network connectivity and fatigue/pain symptoms (Fig. 2b). Higher POMS-fatigue was associated with reduced connectivity between the SMN and DMN ($T = -2.980$, $p_{fdr} = 0.021$) as well as with increased connectivity within the PMN ($T = 2.835$, $p_{fdr} = 0.021$) and between the SMN and PMN ($T = 2.823$, $p_{fdr} = 0.021$; Fig. 2b). These effects were specific to POMS-fatigue as they remained significant when including CIS-fatigue, pain occurrence and RAND-pain as covariates (SMN-DMN: $T = -2.897$, $p_{unc} = 0.005$; PMN-PMN: $T = -2.805$, $p_{unc} = 0.006$; SMN-PMN: $T = -2.584$, $p_{unc} = 0.012$). The relationship between fatigue and SMN-PMN connectivity was further specified by the seed-based analysis. POMS-fatigue symptoms were positively associated with connectivity between the SMN-seed and the SMA ($T = 3.51$, xyz = 14 270, $p_{sv\_fwe\_cluster} = 0.045$; Fig. 2d). Note that this effect was only significant when correcting for the PMN small volume.

Higher RAND-pain was associated with reduced connectivity between PMN and DMN ($T = -3062$, $p_{fdr} = 0.031$). This relationship between pain and PMN-DMN connectivity was not supported by seed-based analysis from the PMN-seed. There was also a non-significant trend for an association between RAND-pain and connectivity between the PMN and FPN ($T = 2.525$, $p_{fdr} = 0.069$) (Fig. 2c). Both remained when including CIS-fatigue, POMS-fatigue and pain occurrence as covariates

Table 1. Clinical symptoms for ME/CFS and HC at baseline

	ME/CFS		HC			
	N	Value (s.e.)	*N*	Value (s.e.)	*T*/*U* value	*p* Value
Baseline						
CIS-fatigue	72	51.7(0.5)	29	16.9(1.3)	30.46	<0.001
POMS-fatigue	72	49.2(2.4)	29	7.0(1.2)	11.07	<0.001
Pain occurrence	67	46.6(3.8)	28	3.8(1.0)	7.27	<0.001
RAND-pain	72	54.8(3.1)	29	91.6(3.0)	−6.92	<0.001
Daily functioning (SIP)	72	1725.6(69.1)				
Depression (BDI-PC)	72	3.7(0.3)	29	1.0(0.3)	4.79	<0.001
Age	72	32.2(1.3)	29	33.2(2.0)	−0.45	ns
Education	72	4.8(0.1)	29	5.1(0.2)	1170	ns

CIS, checklist individual strength; ME/CFS, myalgic encephalomyelitis/Chronic fatigue syndrome; HC, healthy controls; SIP, sickness impact profile; BDI-PC, Beck depression inventory-primary care.

All outcome measures are compared using independent *t* tests, except for education, for which a Mann–Whitney *U* test was done. CIS-fatigue measures fatigue severity of the past 2 weeks. POMS-fatigue measures fatigue across the testing day, RAND-pain measures a combination of pain severity and disability. Note that higher levels are less pain. Pain occurrence measures the % of time one experienced pain-symptoms during the past 2 weeks using diary scores, Daily functioning was measured with the Sickness Impact Profile. Depression was measured with the Beck depression inventory-primary care.

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Table 2. Clinical symptoms for CBT and WL groups at T0, T1, and its difference (T1 – T0)

	CBT		WL			
	N	Value (s.e.)	*N*	Value (s.e.)	*T/U* Value	*p* Value
Baseline/T0						
CIS-fatigue	33	50.9(0.7)	18	51.2(1.3)	−0.19	ns
POMS-fatigue	33	50.2(3.6)	18	46.3(4.0)	0.70	ns
Pain-occurrence	31	50.0(5.3)	16	39.2(8.3)	1.15	ns
RAND-pain	33	55.4(4.8)	18	58.6(6.3)	−0.40	ns
Daily functioning	33	1631.8(88.9)	18	1780.8(186.1)	−0.82	ns
Depression	33	3.5(0.6)	18	4.1(0.6)	−0.74	ns
Age	33	32.9(2.1)	18	29.6(2.5)	0.98	ns
Education	33	4.7(0.3)	18	4.9(0.2)	−0.58	ns
Days between sessions	33	206.8(7.2)	18	186.6(9.6)	1.68	ns
Disease duration	33	5.3(0.3)	18	5.1(0.5)	0.46	ns
T1						
CIS-fatigue	33	33.6(2.6)	18	46.1(1.7)	−3.38	<0.001
POMS-fatigue	33	26.0(3.7)	18	40.7(5.0)	−2.36	<0.05
Pain-occurrence	30	30.5(5.4)	17	34.9(6.9)	−0.50	ns
RAND-pain	33	64.8(4.8)	18	53.5(5.4)	1.48	ns
Daily functioning	33	943.8(118.3)	18	1626.2(184.0)	−3.25	<0.002
Depression	31	1.8(0.4)	18	3.6(0.6)	−2.63	ns
Difference						
CIS-fatigue	33	−17.3(2.7)	18	−5.1(1.6)	−3.22	<0.002
POMS-fatigue	33	−24.2(3.9)	18	−5.5(3.6)	−3.17	<0.003
Pain-occurrence	28	−19.7(5.1)	15	−0.2(2.7)	−2.70	<0.05
RAND-pain	33	+ 9.4(5.1)	18	−5.1(5.2)	1.83	ns
Daily functioning	33	−688.0(125.9)	18	−154.7(97.7)	−2.87	<0.006
Depression	31	−1.8(0.6)	18	−0.6(0.5)	−1.46	ns

CBT, cognitive behavioral therapy; WL, waiting list; CIS, checklist individual strength; SIP, sickness impact profile; BDI-PC, Beck depression inventory-primary care.
CIS-fatigue measures fatigue severity of the past 2 weeks. POMS-fatigue measures fatigue across the testing day, RAND-pain measures a combination of pain severity and disability. Note that higher scores represent lower pain severity and disability. Pain occurrence measures the % of time one experienced pain-symptoms during the past 2 weeks using diary scores, Daily functioning was measured with the sickness impact profile, Depression was measured with the Beck depression inventory-primary care.

(PMN-DMN: $T = 2.717$, $p_{unc} = 0.009$; PMN-FPN: $T = 2.484$, $p_{unc} = 0.016$). Exploratory seed-based analysis supported this trend for PMN-FPN connectivity. Higher levels of both RAND-pain and pain occurrence were associated with lower functional connectivity between the PMN-seed and the left dorsolateral prefrontal cortex (severity: $T = 6.16$, $p_{wb\_fwe\_cluster} < 0.001$, xyz = −401 632; occurrence: $T = 4.53$, $p_{wb\_fwe\_cluster} < 0.002$, xyz = −381 432; Fig. 2e). Note that the p values survived our correction for exploratory whole-brain analyses. The clusters were located within the FPN, but did not overlap with our DLPFC-seed, which was located more anteriorly.

No significant correlations were found between the networks and CIS-fatigue and pain occurrence (Table 4).

Treatment

CBT increased SMN-DMN connectivity compared to the WL ($T = -3.045$, beta = −0.084, $p_{fdr} = 0.038$) (Fig. 3a). Connectivity was increased after CBT ($T = 2.106$, beta = 0.116, $p_{unc} = 0.039$), decreased after the WL ($T = -2.527$, beta = −0.130, $p_{unc} = 0.017$) and did not change in the HC group ($T = -0.976$, beta = −0.040, $p_{unc} = 0.334$). Further post hoc analysis revealed that the CBT and WL group did not differ at baseline/T0 (all $p_{unc} > 0.2$), but SMN-DMN was higher in the CBT compared to the WL group on T1 ($T = -2.697$, beta = −0.062, $p_{unc} = 0.010$) (Table 5). These treatment-group effects were extended by the seed-based analysis (Fig. 3b). Compared to the WL, CBT increased connectivity between SMN-seed and the medial prefrontal cortex (mPFC: $T = 4.28$, $p_{wb\_cluster} < 0.001$, xyz = −14 584) and precuneus ($T = 4.90$, $p_{wb\_cluster} < 0.001$, xyz = 4, −50,30). Seed-based connectivity was increased after CBT (mPFC: $T_{32} = 3.168$, $p = 0.003$; precuneus: $T_{32} = 2.844$, $p = 0.008$), decreased after WL (mPFC; $T_{17} = -4.001$, $p = 0.001$; precuneus: $T_{17} = -3.753$, $p = 0.002$) and did not change in the HC group (mPFC; $T_{23} = -1.280$, $p = 0.21$; precuneus: $T_{23} = 0.625$, $p = 0.54$). Moreover, direct comparisons with the HC group

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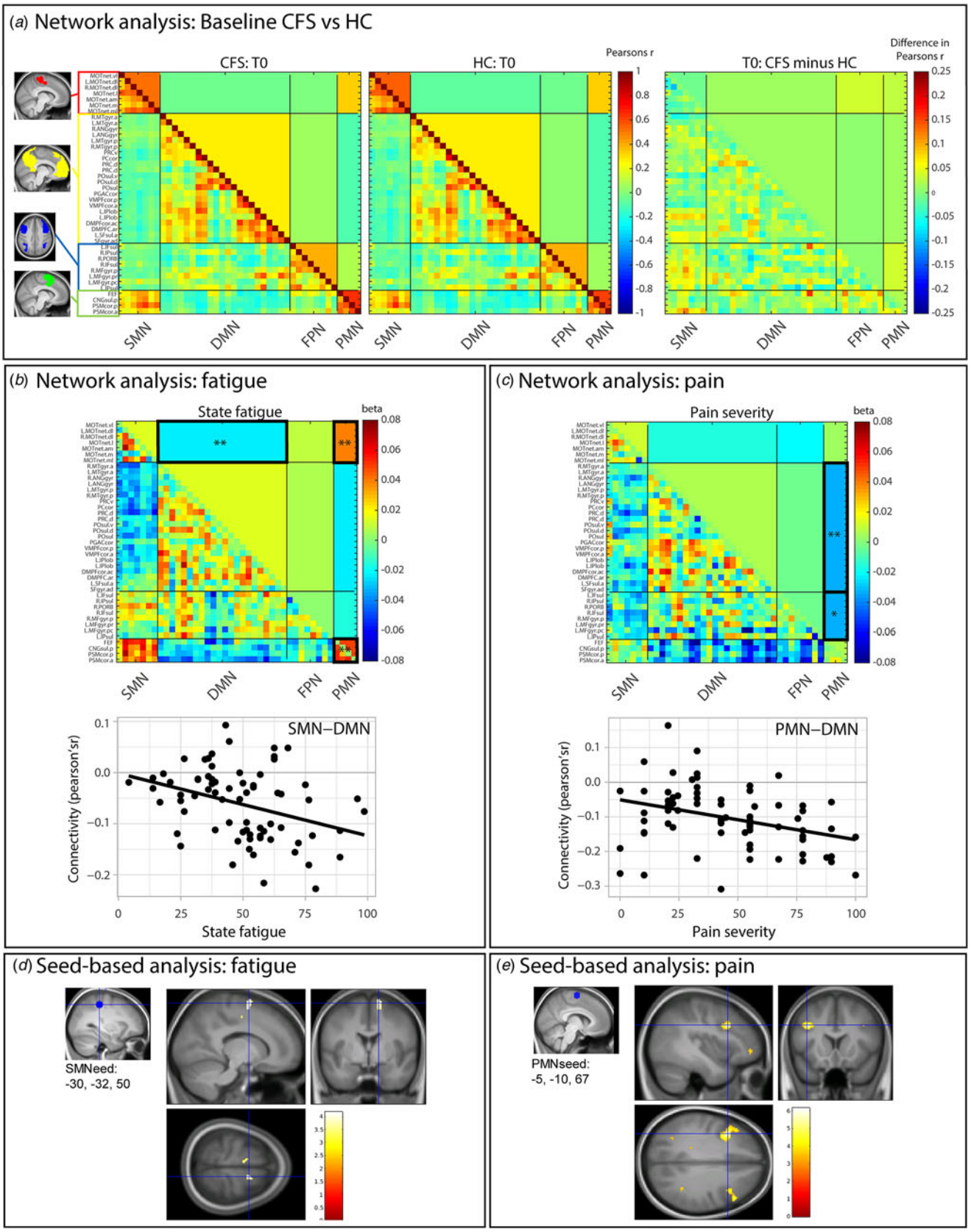

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Figure 2. Baseline results on connectivity measures. (a) Visualization of the four networks that were included in the matrix analysis (all left). Connectivity matrices are shown for the ME/CFS group (left), HC (middle) and the difference between ME/CFS and HC at baseline (right). The lower triangle shows correlations for all regions, the upper triangle shows the reduced matrix with the averaged correlations per network connection. No significant group differences were observed. (b) Beta-values from the regression analysis with state fatigue across the testing day, as measured with the profile of moods state questionnaire, corrected for age and education (upper) and visualization of the correlation between state fatigue across the testing day and SMN-DMN connectivity (lower). (c) Beta-values from the regression analysis with pain severity corrected for age and education (upper) and visualization of the correlation between pain severity and the PMN-DMN network. (d) Results from the seed-based analysis showing regions of which connectivity with the SMN-seed was positively correlated with state fatigue across the testing day ($T = 3.51$, xyz = 14 270, $p_{fwe\_cluster} = 0.045$, small volume corrected for the PMN). This result replicates one of the findings shown in b. (e) Results from the seed-based analysis showing regions of which connectivity with the PMN-seed was positively correlated with pain severity ($T = 6.16$, $p_{wb\_fwe\_cluster} < 0.001$, xyz = −401 632, no small volume correction). This result complements the trend shown in c. Clusters are shown with $p < 0.001$ uncorrected. ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; HC, healthy controls; SMN, Somato motor network; PMN, Premotor network; DMN, Default mode network; FPN, Fronto parietal network. ** $p < 0.05$ fdr-corrected for multiple comparisons, * $p < 0.05$ uncorrected. Abbreviations of the individual regions in the matrix can be found in online Supplementary Table S1.

Table 3. Pearson correlations (s.e.m.) within and between the four networks for ME/CFS and HC at baseline

	T0: Before CBT		
	ME/CFS	HC	*t* Value
Within SMN	0.458 (0.016)	0.475 (0.027)	1.00
Within DMN	−0.011 (0.011)	−0.047 (0.018)	−1.75
Within FPN	0.039 (0.009)	0.032 (0.012)	−0.60
Within PMN	0.516 (0.012)	0.491 (0.021)	−0.89
SMN-DMN	−0.062 (0.008)	−0.073 (0.011)	−0.76
SMN-FPN	0.352 (0.013)	0.327 (0.024)	−0.68
SMN-PMN	−0.103 (0.011)	−0.114 (0.013)	−0.65
DMN-FPN	0.257 (0.006)	0.241 (0.009)	−1.32
DMN-PMN	0.314 (0.011)	0.306 (0.013)	−0.51
FPN-PMN	0.076 (0.012)	0.042 (0.019)	−1.41

SMN, somato-motor network; DMN, default mode network; FPN, fronto-parietal network; PMN, premotor network; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; HC, healthy controls.
None of the group comparisons were significant.

(group by time interactions) revealed that the increase in SMNseed-mPFC connectivity was driven by the CBT group (CBT *v.* HC: $F_{53,1} = 7.535$, $p = 0.008$; WL *v.* HC: $F_{38,1} = 4178$, $p = 0.048$), while the change in SMN-seed-precuneus connectivity was driven by the WL group (WL *v.* HC: $F_{38,1} = 6.428$, $p = 0.015$; CBT *v.* HC: $F_{53,1} = 1.399$, $p = 0.24$).

Regression analysis within the CBT group on extracted data from these mPFC and precuneus clusters revealed that reductions in fatigue and pain were only associated with increased SMN-seed-mPFC connectivity (ΔCIS-fatigue: $R^2 = 0.20$, beta = −0.46, $T_{3,29} = -2.651$, $p = 0.013$; ΔState-fatigue: $R^2 = 0.17$, beta = −0.42, $T_{3,29} = -2.407$, $p = 0.023$; Δpain-Occurrence: $R^2 = 0.20$, beta = −0.47, $T_{3,24} = -2.328$, $p = 0.029$; but not ΔRand-pain: $R^2 = 0.053$, beta = 0.24, $T_{3,29} = 1.253$, $p = 0.220$) (Fig. 3d) and not with changes in SMN-seed-precuneus connectivity (all $p > 0.05$). These changes were not specific to either pain or fatigue: none of the covariates remained significant when all 4 variables were included into one model (all $p > 0.05$). Regression analysis within the CBT group on data from the network analysis did not yeald any signifIcant relationships with symptom measures (Table 6).

Discussion

This study aimed to dissociate neural networks associated with pain and fatigue symptoms in in ME/CFS. Results revealed partly dissociable networks, with modality specific involvement of sensory-motor networks in fatigue (SMN-DMN) and premotor networks in pain (PMN-DMN), and common involvement of the DMN. CBT led to improvements in both fatigue and pain, compared to WL, which were associated with increased prefrontal

Table 4. Beta values of the relationships between connectivity (*z* scored Pearson correlation) and the four covariates of interest within the ME/CFS group at baseline

	T0: Before CBT			
	CIS-fatigue	Fatigue on testing day	Pain severity	Pain occurrence
Within SMN	−0.008	0.014	0.010	−0.033
Within DMN	0.01	0.013	0.007	−0.006
Within FPN	0.005	0.001	−0.004	−0.013
Within PMN	0.007	**0.048 ****	0.007	−0.014
SMN-DMN	−0.009	**−0.024 ****	−0.016	0.009
SMN-FPN	0.016	0.008	−0.021	0.012
SMN-PMN	0.009	**0.040 ****	0.003	−0.013
DMN-FPN	−0.005	0.005	−0.003	−0.002
DMN-PMN	−0.012	−0.025 *	**−0.034 ****	0.013
FPN-PMN	0.008	−0.015	−0.033 *	0.021

SMN, somato-motor network; DMN, default mode network; FPN, fronto-parietal network; PMN, premotor network. Fatigue on testing day was measured using the Profile of Mood State questionnaire (POMS)
Age and education were included as covariates of no interest. ** $p < 0.05$ fdr corrected for multiple comparison, * $p < 0.05$ uncorrected.

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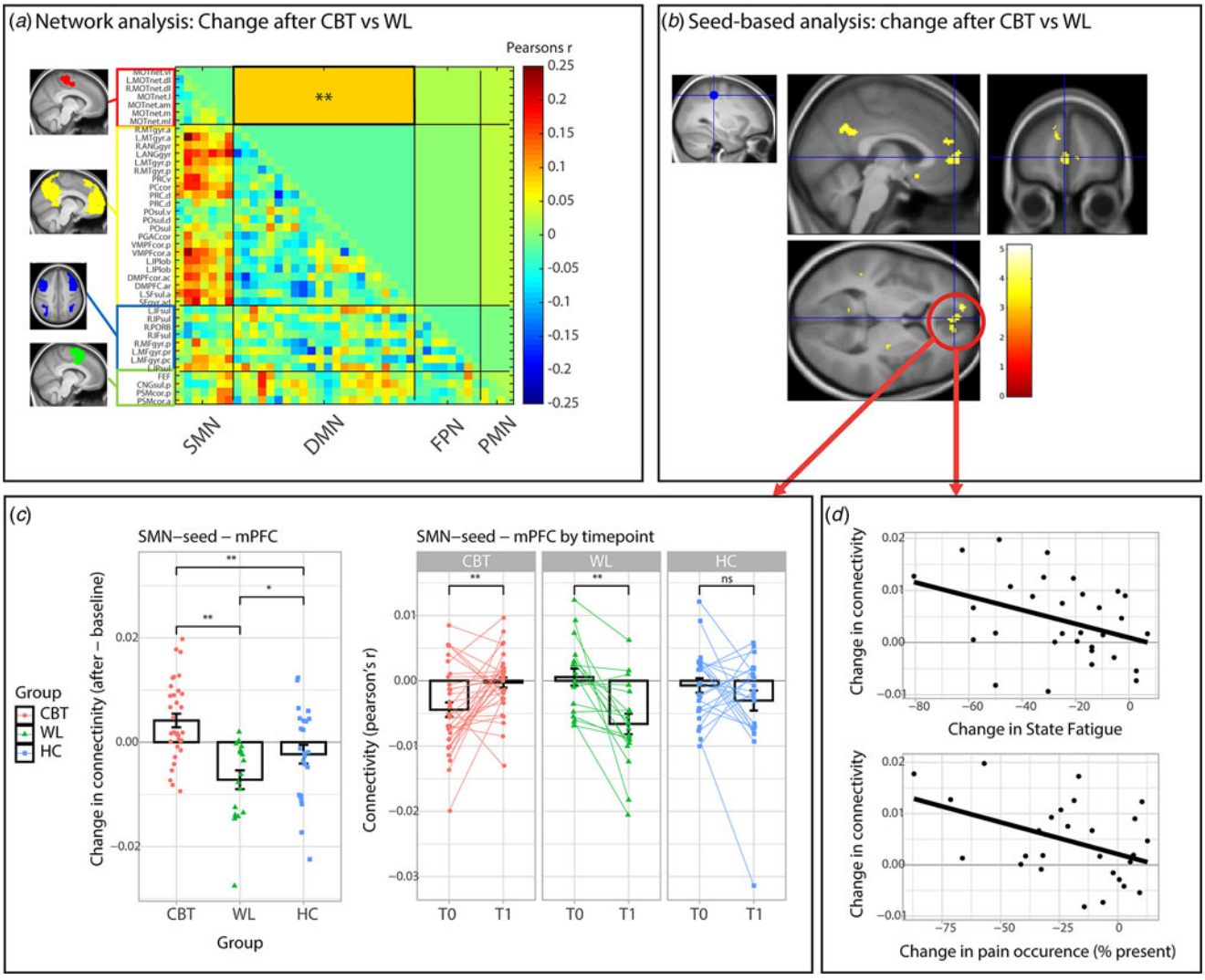

Figure 3. Treatment effects (T1 minus T0) on connectivity measures. (a) Visualization of the four networks that were included in the matrix analysis (all left). Change in connectivity (T1 minus T0) is shown for CBT *v.* WL. The lower triangle shows correlations for all regions, the upper triangle shows the reduced matrix with the averaged correlations per network connection. CBT significantly increased connectivity between SMN and DMN compared to WL ($T = -3.045$, beta = −0.084, $p_{fdr} = 0.038$). ** $p < 0.05$ fdr-corrected for multiple comparisons. (b) Confirmation of the network analysis by the seed-based analysis using the SMN-seed (left). CBT increased connectivity in the mPFC and Precuneus compared to WL. (c) Visualization of the change in SMNseed-mPFC connectivity in the CBT, WL, and HC groups. An increase in SMNseed-mPFC connectivity was driven by the CBT group (CBT *v.* HC: $F_{53,1} = 7.535$, $p = 0.008$), while a smaller decrease was observed for the WL group (WL *v.* HC: $F_{38,1} = 4178$, $p = 0.048$). * = $p < 0.05$, ** = $p < 0.01$, ns, not significant. (d) Correlations between SMNseed-mPFC connectivity and the clinical measures state fatigue across the testing day (beta = −0.42, $p = 0.023$) and pain occurrence (beta = −0.47, $p = 0.029$) within the CBT group. CBT, cognitive behavioral therapy; WL, waiting list; SMN, somato motor network; PMN, premotor network; DMN, default mode network; FPN, fronto parietal network; mPFC, medial prefrontal cortex. ** $p < 0.05$ fdr-corrected for multiple comparisons, * $p < 0.05$ uncorrected. Abbreviations of the individual regions in the matrix can be found in online Supplementary Table S1.

(i.e. mPFC within the DMN) modulation of the fatigue-related SMN, but not of the pain-related PMN. These results progress the ME/CFS field in several ways. First, they highlight the need for better understanding of the differential role of these networks in the etiology of fatigue and pain symptoms in ME/CFS, in order to better tailor treatments to these symptoms. Second, they provide insight on the mechanisms of change in CBT-responsive patients, but also provide new leads toward improving and individualizing existing treatments or develop new (non-behavioral) treatments.

Results showed that communication of the SMN with the PMN and DMN was specifically associated with between-participants variance in fatigue across the testing day, over and above the contribution of variance related to pain occurrence, pain disability and CIS-fatigue. This is in line with our hypothesis and previous reports on sensorimotor involvement in fatigue in multiple sclerosis (MS) (Hidalgo de la Cruz et al., 2018), stroke (De Doncker, Dantzer, Ormstad, & Kuppuswamy, 2018; Kuppuswamy, Rothwell, & Ward, 2015), perinatal stroke (Wrightson, Zewdie, Kuo, Millet, & Kirton, 2020) and ankylosing spondylitis (Liu et al., 2020) and generalize our previously reported task-related effects of fatigue (van der Schaaf et al., 2018) to resting-state connectivity. The lack of relationship with CIS-fatigue may relate to the low variability in CIS-fatigue scores as patients were selected to be severely fatigued on this score. It may also suggest that SMN-PMN connectivity more likely reflects the daily fatigue, rather than overall fatigue measured retrospectively across 2 weeks. Daily fatigue was measured as the average

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Table 5. Change in Fisher's *z* transformed correlations (S.E.M.) within and between the four networks for CBT, WL, and HC.

	T1 minus T0					
	CBT	WL	HC	*t* value CBT *v.* WL	*t* value CBT *v.* HC	*t* value WL *v.* HC
Within SMN	0.071 (0.03)	0.081 (0.048)	−0.042 (0.038)	0.241	−2.585 *	−2.347 *
Within DMN	−0.006 (0.019)	−0.025 (0.024)	0.004 (0.021)	−0.817	0.203	1.053
Within FPN	0.01 (0.013)	0.009 (0.019)	0.005 (0.015)	−0.037	−0.131	−0.046
Within PMN	0.011 (0.031)	−0.026 (0.04)	−0.014 (0.034)	−0.711	−0.313	0.238
SMN-DMN	0.027 (0.015)	−0.053 (0.023)	0.001 (0.014)	**−3.045 ** **	−1.215	2.135 *
SMN–FPN	0.051 (0.026)	0.013 (0.032)	0.002 (0.029)	−0.953	−1.395	−0.445
SMN–PMN	0.033 (0.016)	0.005 (0.026)	0.018 (0.017)	−1.016	−0.559	0.621
DMN–FPN	−0.029 (0.011)	−0.002 (0.014)	−0.021 (0.013)	1.758	0.406	−1.139
DMN-PMN	−0.019 (0.016)	0.014 (0.029)	−0.017 (0.017)	1.18	0.169	−0.952
FPN–PMN	0.009 (0.02)	0.015 (0.021)	0.001 (0.025)	−0.05	−0.279	−0.192

SMN, somato-motor network; DMN, default mode network; FPN, fronto-parietal network; PMN, premotor network; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; HC, healthy controls.
** $p < 0.05$ fdr corrected for multiple comparisons. * $p < 0.05$ uncorrected.

Table 6. Beta values of the relationships between the change in connectivity (*z* scored Pearsons correlation) and the change in the four covariates of interest within the CBT group

	T1 minus T0 (within the CBT group)			
	ΔCIS-fatigue	Δfatigue on testing day	ΔPain severity	ΔPain occurrence
Within SMN	0.039	0.006	0.035	−0.205
Within DMN	0.016	0.01	0.018	−0.044
Within FPN	0.007	0.014	−0.016	−0.323
Within PMN	0.008	−0.01	0.025	−0.355
SMN-DMN	−0.016	−0.004	−0.029 *	−0.045
SMN-FPN	0.004	0.018	−0.006	−0.697
SMN-PMN	0.021	−0.009	0.015	−0.492
DMN-FPN	0.011	0.004	−0.023 *	−0.04
DMN-PMN	−0.002	0.008	−0.036 *	−0.014
FPN-PMN	−0.02	−0.006	−0.011	−0.502

SMN, somato-motor network; DMN, default mode network; FPN, fronto-parietal network; PMN, premotor network. Fatigue on testing day was measured using the Profile of Mood State questionnaire (POMS)
Age and education were included as covariates of no interest. ** $p < 0.05$ fdr corrected for multiple comparisons, * $p < 0.05$ uncorrected.

score on the POMS-subscale fatigue across three measurements during the test day. It was higher and more variable in ME/CFS patients compared to HC and reduced after CBT compared to WL. Accordingly this measure of overall fatigue during the testing day likely also captures clinical aspects of fatigue that was independent from patient selection.

Alterations in sensorimotor function have been linked physiological fatigue after 40 min on a bicycle ergometer (Hu et al., 2022) and effort-perception (Zenon, Sidibe, & Olivier, 2015). Specifically, current neurobiological accounts state that fatigue and high effort perception arise when sensory consequences of actions (processed in sensorimotor regions) do not match the proprioceptive prediction (i.e. the efference copy signaled by the SMA) (Greenhouse-Tucknott et al., 2022; Kuppuswamy, 2021; Stephan et al., 2016). Thus, when muscle performance reduces after prolonged activity, compared to the initially planned or desired performance, a prediction error occurs, signaling fatigue. The observed increase in connectivity between premotor and sensorimotor networks may therefore reflect altered communication between the SMA that signals intended actions plans and the SMN that signals the actual sensory consequence of those actions. It might be possible that the resulting prediction errors arise quicker in ME/CFS patients, or are not adequately resolved by rest. This could explain the elevated sense of effort and prolonged recovery time after exercise in ME/CFS patients (Barhorst et al., 2020). To further investigate this, future research could assess sensorimotor functioning during and after physical exertions tasks.

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In line with our hypotheses and a previous study linking DLPFC gray matter volume in ME/CFS to pain rather than fatigue (van der Schaaf et al., 2017), the current study also suggests modality specific involvement of DLPFC connectivity in pain. There was a non-significant trend for a relationship between pain and PMN-FPN connectivity, and seed-based analysis further specified that SMA-DLPFC connectivity was driven by RAND-pain and pain-occurrence and not by CIS-fatigue or POMS-fatigue. DLPFC's connection with premotor regions has recently been associated with movement-evoked pain in chronic low back pain patients (Wang et al., 2021). Moreover, a meta-analysis linked SMA and premotor regions to pain-related motor function, while its connection with the DLPFC is important for selecting appropriate responses to pain (de la Vega, Chang, Banich, Wager, & Yarkoni, 2016). Accordingly, this connection potentially relates to the motor consequences of pain symptoms, which is consistent with the RAND-pain measure which not only assesses pain severity, but also its impact on daily activities.

Lower connectivity of the DMN with the SMN and PMN were associated with more fatigue and pain symptoms, respectively. This is in line with reports of decreased DMN connectivity with non-DMN networks in both pain and fatigue pathologies (Davis & Moayedi, 2013; Farmer et al., 2012; Maksoud et al., 2020). We hypothesized that CBT would also differentially modulate fatigue and pain related connections (i.e. DMN-SMN and DMN-PMN, respectively), but this is not what we observed. Instead, we observed that CBT-induced clinical improvements in both fatigue and pain (i.e. CIS-fatigue, POMS-fatigue, and pain occurrence) were related to increased connectivity between the frontal DMN and the fatigue-related SMN. Direct comparison with HC revealed that these changes of frontal DMN connectivity (i.e. mPFC) occurred in the CBT and not the WL group. Together, this suggests successful CBT involves frontal DMN modulation of modality specific fatigue-related cortical networks

The DMN and vmPFC have been associated with the evaluation of current and future bodily states (Gottfried, O'Doherty, & Dolan, 2003; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; Robinson & Berridge, 2013; Wagner, Rutgen, Hummer, Windischberger, & Lamm, 2020) which modulates sensory perception and motivated behavior, through their connections with sensorimotor and premotor regions (Adams, Shipp, & Friston, 2013; Ashar, Chang, & Wager, 2017; Bar, 2007; Dohmatob, Dumas, & Bzdok, 2020; Geuter, Koban, & Wager, 2017). This makes it a central network that is particularly important for allostasis i.e. the ability to control behavior (including autonomic responses) in anticipation of homeostatic disturbances (Ashar et al., 2017; Geuter et al., 2017; Stephan et al., 2016). The observed reduced connectivity of the DMN with PMN and SMN in patients with more pain and fatigue may therefore point toward suboptimal integration of anticipated consequences of actions on bodily states and current sensory/introspective processing and motor planning. At a behavioral level, this may result in biased action-selections that depend on anticipated effort-costs or pain, including avoidance of activities that are expected to cause (too much) fatigue or pain (Becker, Gandhi, & Schweinhardt, 2012; Hogan, Chen, Teh, & Chib, 2020; Iodice et al., 2017; Kuppuswamy, 2021; Lacourt et al., 2018a; Muller, Klein-Flugge, Manohar, Husain, & Apps, 2021; van der Schaaf et al., 2018). CBT may be effective (at least in a subset of patients) by regaining the modulatory role of the vmPFC on sensory-motor regions, thereby reducing discrepancies between anticipated and actual sensory consequences of actions. Indeed, CBT for ME/CFS aims to reduce fatigue by changing cognitions and expectations about fatigue-related activities, to ultimately reduce fatigue and improve self-efficacy to control fatigue. As CBT was focused on fatigue, rather than pain, it may have more strongly affected the fatigue related SMN network. Alternatively, SMN modulation may have simultaneously reduced pain by altering sensory processing of pain. Unfortunately, as changes in fatigue and pain were highly correlated, we cannot state whether the change in SMN-DMN connectivity reflects the change in both symptoms or in fatigue only. Additionally, as CBT was compared to a WL condition, it remains to be determined whether these effects are specific to CBT or whether other (behavioral) treatments may have similar effects.

Some limitations of the current study need to be addressed. First, limiting analysis to a selection of a priori defined networks (van der Schaaf et al., 2017; van der Schaaf et al., 2018), may have excluded some pain- or fatigue-related regions. However, exploratory uncorrected whole brain analyses (online Supplementary Results and Figs S3–S6) confirmed our main results and point toward potential involvement of cerebellar, basal ganglia and mesolimbic networks which require further confirmation in new independent samples.

Second, in contrast to our expectations, there were no baseline differences between ME/CFS patients and healthy controls. One possibility is that only a subset of ME/CFS patients shows reduced connectivity at baseline, and that this did not surface in a group comparison. This may limit conclusions about a clear disease-related pathology. Another reason for a lack of difference is that ME/CFS is a heterogeneous condition and involves various symptoms that contribute with varying extend to the clinical presentation of ME/CFS. The substantial individual variability in symptom profiles may result in variable changes across brain networks that may not surface in a group comparison (van der Schaaf et al., 2017).

The main aim of this study was to gain insight into symptom specific pathology in ME/CFS and to identify partly dissociable patterns of neural connectivity for pain and fatigue symptoms. This requires assessment of the relationships between (changes in) symptoms and (changes in) connectivity measures within the patient group itself (Kuppuswamy, 2023), rather than a group comparison with healthy controls. The lack of group differences and presence of symptom specific associations further highlights the need for a multidimensional approach to ME/CFS, where various combinations of symptoms expressions may relate to different underlying (neuro)biological pathologies.

Although the current study used the U.S. Centers for Disease Control (CDC)-criteria for ME/CFS (revised in 2003) (Fukuda et al., 1994; Reeves et al., 2003), as preregistered (van Der Schaaf et al., 2015), there was considerable overlap with the Canadian and Institute of Medicine criteria (see the online Supplement of van der Schaaf et al. (2017). Accordingly, similar variability in symptoms is expected from alternative ME/CFS criteria.

Third, CBT was only effective in a subset of patients and only affected some neural networks, highlighting the need to further investigate why some patients benefit from CBT and others do not. In addition, as baseline results were correlational no causality can be inferred. It remains unclear whether altered connectivity reflected a 'central' or cognitive problem, or whether it results from persistent peripheral abnormalities. Studies assessing in whom and to what extend neural networks and symptoms are affected by central and peripheral causes are therefore warranted. While the former could be effectively treated by CBT or non-invasive brain-stimulation of sensorimotor regions (Ashrafi, Mohseni-Bandpei, & Seydi, 2020; Cancelli et al., 2018; Porcaro

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et al., 2019; Zenon et al., 2015), the latter would require a better understanding of potential biological factors that may underlie ME/CFS (Proal & VanElzakker, 2021), including altered immune function (Raijmakers et al., 2019a; Raijmakers et al., 2019b; Raijmakers et al., 2020; VanElzakker, Brumfield, & Lara Mejia, 2018), altered expression of the tryptophan-catabolizing enzyme indoleamine 2,3-dioxygenase-2 (IDO2) (Guo et al., 2023), changes in energy metabolism (Lacourt, Vichaya, Chiu, Dantzer, & Heijnen, 2018b), muscle function (Soares et al., 2022) and/or (neuro) inflammation (Albrecht et al., 2019; Nakatomi et al., 2014; Nieuwland et al., 2023) (but see (Raijmakers et al., 2022). Together, this could ultimately improve and individualize both existing treatments, while also providing insights for new treatment-targets.

Using the largest sample of ME/CFS patients to date, this study highlights specific roles for SMN and DLPFC connectivity in fatigue and pain symptoms, respectively, that are commonly modulated by the DMN. CBT may reduce symptoms in CBT-responsive patients by altering DMN modulation of modality specific networks. Further investigation of the specific roles of these networks in fatigue and pain symptoms and how they are affected by cognitive and/or biological factors are warranted to better individualize existing and new treatments for ME/CFS.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003690

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References

Aaron, L., Herrell, R., Ashton, S., Belcourt, M., Schmaling, K., Goldberg, J., & Buchwald, D. (2001). Comorbid clinical conditions in chronic fatigue. A co-twin control study. *Journal of General Internal Medicine*, *16*(1), 24–31.

Aaronson, N. K., Muller, M., Cohen, P. D., Essink-Bot, M. L., Fekkes, M., Sanderman, R., … Verrips, E. (1998). Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. *Journal of Clinical Epidemiology*, *51*(11), 1055–1068. https://doi.org/10.1016/s0895-4356(98)00097-3

Adams, R. A., Shipp, S., & Friston, K. J. (2013). Predictions not commands: Active inference in the motor system. *Brain Structure and Function*, *218*(3), 611–643. https://doi.org/10.1007/s00429-012-0475-5

Albrecht, D. S., Forsberg, A., Sandstrom, A., Bergan, C., Kadetoff, D., Protsenko, E., … Loggia, M. L. (2019). Brain glial activation in fibromyalgia: A multi-site positron emission tomography investigation. *Brain Behaviour and Immunity*, *75*, 72–83. https://doi.org/10.1016/j.bbi.2018.09.018

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*, *9*(4), 463–484. https://doi.org/10.1016/j.ejpain.2004.11.001

Ashar, Y. K., Chang, L. J., & Wager, T. D. (2017). Brain mechanisms of the placebo effect: An affective appraisal account. *Annual Review of Clinical Psychology*, *13*, 73–98. https://doi.org/10.1146/annurev-clinpsy-021815-093015

Ashrafi, A., Mohseni-Bandpei, M. A., & Seydi, M. (2020). The effect of tDCS on the fatigue in patients with multiple sclerosis: A systematic review of randomized controlled clinical trials. *Journal of Clinical Neuroscience*, *78*, 277–283. https://doi.org/10.1016/j.jocn.2020.04.106

Baliki, M. N., Mansour, A. R., Baria, A. T., & Apkarian, A. V. (2014). Functional reorganization of the default mode network across chronic pain conditions. *PLoS One*, *9*(9), e106133. https://doi.org/10.1371/journal.pone.0106133

Bar, M. (2007). The proactive brain: Using analogies and associations to generate predictions. *Trends in Cognitive Sciences*, *11*(7), 280–289. https://doi.org/10.1016/j.tics.2007.05.005

Barhorst, E. E., Andrae, W. E., Rayne, T. J., Falvo, M. J., Cook, D. B., & Lindheimer, J. B. (2020). Elevated perceived exertion in people with myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia: A meta-analysis. *Medicine and Science in Sports and Exercise*, *52*(12), 2615–2627. https://doi.org/10.1249/MSS.0000000000002421

Becker, S., Gandhi, W., & Schweinhardt, P. (2012). Cerebral interactions of pain and reward and their relevance for chronic pain. *Neuroscience Letters*, *520*(2), 182–187. https://doi.org/10.1016/j.neulet.2012.03.013

Bergner, M., Bobbitt, R. A., Carter, W. B., & Gilson, B. S. (1981). The sickness impact profile: Development and final revision of a health status measure. *Medical care*, *19*(8), 787–805.

Boissoneault, J., Letzen, J., Lai, S., O'Shea, A., Craggs, J., Robinson, M. E., & Staud, R. (2016). Abnormal resting state functional connectivity in patients with chronic fatigue syndrome: An arterial spin-labeling fMRI study. *Magnetic Resonance Imaging*, *34*(4), 603–608. https://doi.org/10.1016/j.mri.2015.12.008

Buchel, C., Geuter, S., Sprenger, C., & Eippert, F. (2014). Placebo analgesia: A predictive coding perspective. *Neuron*, *81*(6), 1223–1239. https://doi.org/10.1016/j.neuron.2014.02.042

Buchwald, D., Pearlman, T., Kith, P., Katon, W., & Schmaling, K. (1997). Screening for psychiatric disorders in chronic fatigue and chronic fatigue symdrome. *Psychosomatic Research*, *42*(1), 87–94.

Cancelli, A., Cottone, C., Giordani, A., Migliore, S., Lupoi, D., Porcaro, C., … Tecchio, F. (2018). Personalized, bilateral whole-body somatosensory cortex stimulation to relieve fatigue in multiple sclerosis. *Multiple Sclerosis*, *24*(10), 1366–1374. https://doi.org/10.1177/1352458517720528

Castro-Marrero, J., Faro, M., Aliste, L., Saez-Francas, N., Calvo, N., Martinez-Martinez, A., … Alegre, J. (2017). Comorbidity in chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide population-based cohort study. *Psychosomatics*, *58*(5), 533–543. https://doi.org/10.1016/j.psym.2017.04.010

Davis, K. D. (2000). The neural circuitry of pain as explored with functional MRI. *Neurological Research*, *22*(3), 313–317. https://doi.org/10.1080/01616412.2000.11740676

Davis, K. D., & Moayedi, M. (2013). Central mechanisms of pain revealed through functional and structural MRI. *Journal of Neuroimmune Pharmacology*, *8*(3), 518–534. https://doi.org/10.1007/s11481-012-9386-8

De Doncker, W., Dantzer, R., Ormstad, H., & Kuppuswamy, A. (2018). Mechanisms of poststroke fatigue. Journal of Neurology, *Neurosurgery and Psychiatry*, *89*(3), 287–293. https://doi.org/10.1136/jnnp-2017-316007

de la Vega, A., Chang, L. J., Banich, M. T., Wager, T. D., & Yarkoni, T. (2016). Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. *Journal of Neuroscience*, *36*(24), 6553–6562. https://doi.org/10.1523/JNEUROSCI.4402-15.2016

Dohmatob, E., Dumas, G., & Bzdok, D. (2020). Dark control: The default mode network as a reinforcement learning agent. *Human Brain Mapping*, *41*(12), 3318–3341. https://doi.org/10.1002/hbm.25019

Fallon, N., Chiu, Y., Nurmikko, T., & Stancak, A. (2016). Functional connectivity with the default mode network is altered in fibromyalgia patients. *PLoS One*, *11*(7), e0159198. https://doi.org/10.1371/journal.pone.0159198

Farmer, M. A., Baliki, M. N., & Apkarian, A. V. (2012). A dynamic network perspective of chronic pain. *Neuroscience Letters*, *520*(2), 197–203. https://doi.org/10.1016/j.neulet.2012.05.001

Friston, K. J., Glaser, D. E., Henson, R. N., Kiebel, S., Phillips, C., & Ashburner, J. (2002). Classical and Bayesian inference in neuroimaging: Applications. *Neuroimage*, *16*(2), 484–512. https://doi.org/10.1006/nimg.2002.1091

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*(12), 953–959.

Gay, C. W., Robinson, M. E., Lai, S., O'Shea, A., Craggs, J. G., Price, D. D., & Staud, R. (2016). Abnormal resting-state functional connectivity in patients with chronic fatigue syndrome: Results of seed and data-driven analyses. *Brain Connectivity*, *6*(1), 48–56. https://doi.org/10.1089/brain.2015.0366

Geerligs, L., Cam, C., & Henson, R. N. (2016). Functional connectivity and structural covariance between regions of interest can be measured more accurately using multivariate distance correlation. *Neuroimage*, *135*, 16–31. https://doi.org/10.1016/j.neuroimage.2016.04.047

Geerligs, L., Cam, C. A. N., & Campbell, K. L. (2018). Age-related differences in information processing during movie watching. *Neurobiological Aging*, *72*, 106–120. https://doi.org/10.1016/j.neurobiolaging.2018.07.025

Geerligs, L., Tsvetanov, K. A., Cam, C., & Henson, R. N. (2017). Challenges in measuring individual differences in functional connectivity using fMRI: The case of healthy aging. *Human Brain Mapping*, *38*(8), 4125–4156. https://doi.org/10.1002/hbm.23653

Geuter, S., Koban, L., & Wager, T. D. (2017). The cognitive neuroscience of placebo effects: Concepts, predictions, and physiology. *Annual Review of Neuroscience*, *40*, 167–188. https://doi.org/10.1146/annurev-neuro-072116-031132

Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science (New York, N.Y.)*, *301*(5636), 1104–1107. https://doi.org/10.1126/science.1087919

Greenhouse-Tucknott, A., Butterworth, J. B., Wrightson, J. G., Smeeton, N. J., Critchley, H. D., Dekerle, J., & Harrison, N. A. (2022). Toward the unity of pathological and exertional fatigue: A predictive processing model. *Cognitive Affective Behavioural Neuroscience*, *22*(2), 215–228. https://doi.org/10.3758/s13415-021-00958-x

Guo, L., Appelman, B., Mooij-Kalverda, K., Houtkooper, R. H., van Weeghel, M., Vaz, F. M., … Amsterdam UMCC-BsG. (2023). Prolonged indoleamine 2,3-dioxygenase-2 activity and associated cellular stress in post-acute sequelae of SARS-CoV-2 infection. *EBioMedicine*, *94*, 104729. https://doi.org/10.1016/j.ebiom.2023.104729

Hare, T. A., O'Doherty, J., Camerer, C. F., Schultz, W., & Rangel, A. (2008). Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. *Journal of Neuroscience*, *28*(22), 5623–5630. https://doi.org/10.1523/JNEUROSCI.1309-08.2008

Hidalgo de la Cruz, M., d'Ambrosio, A., Valsasina, P., Pagani, E., Colombo, B., Rodegher, M., … Rocca, M. A. (2018). Abnormal functional connectivity of thalamic sub-regions contributes to fatigue in multiple sclerosis. *Multiple Sclerosis*, *24*(sssss9), 1183–1195. https://doi.org/10.1177/1352458517717807

Hogan, P. S., Chen, S. X., Teh, W. W., & Chib, V. S. (2020). Neural mechanisms underlying the effects of physical fatigue on effort-based choice. *Nature Communications*, *11*(1), 4026. https://doi.org/10.1038/s41467-020-17855-5

Hu, E. J., Casamento-Moran, A., Galaro, J. K., Chan, K. L., Edden, R. A. E., Puts, N. A. J., & Chib, V. S. (2022). Sensorimotor cortex GABA moderates the relationship between physical exertion and assessments of effort. *Journal of Neuroscience*, *42*(31), 6121–6130. https://doi.org/10.1523/JNEUROSCI.2255-21.2022

Iodice, P., Ferrante, C., Brunetti, L., Cabib, S., Protasi, F., Walton, M. E., & Pezzulo, G. (2017). Fatigue modulates dopamine availability and promotes flexible choice reversals during decision making. *Scientific Reports*, *7*(1), 535. https://doi.org/10.1038/s41598-017-00561-6

Kim, B. H., Namkoong, K., Kim, J. J., Lee, S., Yoon, K. J., Choi, M., & Jung, Y. C. (2015a). Altered resting-state functional connectivity in women with chronic fatigue syndrome. *Psychiatry Research*, *234*(3), 292–297. https://doi.org/10.1016/j.pscychresns.2015.10.014

Kim, J., Loggia, M. L., Cahalan, C. M., Harris, R. E., Beissner, F. D. P. N., Garcia, R. G., … Napadow, V. (2015b). The somatosensory link in fibromyalgia: Functional connectivity of the primary somatosensory cortex is altered by sustained pain and is associated with clinical/autonomic dysfunction. *Arthritis Rheumatology*, *67*(5), 1395–1405. https://doi.org/10.1002/art.39043

Knoop, H., Bleijenberg, G., Gielissen, M. F., van der Meer, J. W., & White, P. D. (2007). Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? *Psychotherapy and Psychosomatics*, *76*(3), 171–176. https://doi.org/10.1159/000099844

Kong, J., Spaeth, R. B., Wey, H. Y., Cheetham, A., Cook, A. H., Jensen, K., … Gollub, R. L. (2013). S1 is associated with chronic low back pain: A functional and structural MRI study. *Molecular Pain*, *9*, 43. https://doi.org/10.1186/1744-8069-9-43

Krupp, L., Jandorp, L., Coyle, P., & Mendelson, W. (1993). Sleepdisturbance in chronic fatigue syndrome. *Journal of Psychosomatic Research*, *37*(4), 325–331.

Kuppuswamy, A. (2021). The neurobiology of pathological fatigue: New models, new questions. *Neuroscientist*, 1–16. https://doi.org/10.1177/1073858420985447

Kuppuswamy, A. (2023). On the importance of not comparing apples with pears. *European Journal of Neurology*, *30*(2), 557. https://doi.org/10.1111/ene.15587

Kuppuswamy, A., Rothwell, J., & Ward, N. (2015). A model of poststroke fatigue based on sensorimotor deficits. *Current Opinion in Neurology*, *28*(6), 582–586. https://doi.org/10.1097/WCO.0000000000000260

Lacourt, T., Vichaya, E., Chiu, G., Dantzer, R., & Heijnen, C. (2018b). The high costs of low-grade inflammation: Persistent fatigue as a consequence of reduced cellular-energy availability and non-adaptive energy expenditure. *Frontiers in Behavioural Neuroscience*, *12*, 78. https://doi.org/10.3389/fnbeh.2018.00078

Lacourt, T. E., Vichaya, E. G., Escalante, C., Manzullo, E. F., Gunn, B., Hess, K. R., … Dantzer, R. (2018a). An effort expenditure perspective on cancer-related fatigue. *Psychoneuroendocrinology*, *96*, 109–117. https://doi.org/10.1016/j.psyneuen.2018.06.009

Liu, Q., Liao, Z., Zhang, Y., Lin, C., He, B., Fang, L., … Gu, J. (2020). Pain- and fatigue-related functional and structural changes in ankylosing spondylitis: An fRMI study. *Frontiers in Medicine*, *7*, 193. https://doi.org/10.3389/fmed.2020.00193

Maksoud, R., du Preez, S., Eaton-Fitch, N., Thapaliya, K., Barnden, L., Cabanas, H., … Marshall-Gradisnik, S. (2020). A systematic review of neurological impairments in myalgic encephalomyelitis/ chronic fatigue syndrome using neuroimaging techniques. *PLoS One*, *15*(4), e0232475. https://doi.org/10.1371/journal.pone.0232475

Malouff, J. M., Thorsteinsson, E. B., Rooke, S. E., Bhullar, N., & Schutte, N. S. (2008). Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta-analysis. *Clinical Psychology Review*, *28*(5), 736–745. https://doi.org/10.1016/j.cpr.2007.10.004

McNair, D., Lorr, M., & Doppleman, L. (1971). *POMS Manual for the profile of mood states*. San Diego, CA: Educational and Industrial Testing Service.

Muller, T., & Apps, M. A. J. (2019). Motivational fatigue: A neurocognitive framework for the impact of effortful exertion on subsequent motivation. *Neuropsychologia*, *123*, 141–151. https://doi.org/10.1016/j.neuropsychologia.2018.04.030

Muller, T., Klein-Flugge, M. C., Manohar, S. G., Husain, M., & Apps, M. A. J. (2021). Neural and computational mechanisms of momentary fatigue and persistence in effort-based choice. *Nature Communications*, *12*(1), 4593. https://doi.org/10.1038/s41467-021-24927-7

Nakatomi, Y., Mizuno, K., Ishii, A., Wada, Y., Tanaka, M., Tazawa, S., … Watanabe, Y. (2014). Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: An (1)(1)C-(R)-PK11195 PET study. *Journal of Nuclear Medicine*, *55*(6), 945–950. https://doi.org/10.2967/jnumed.113.131045

Nieuwland, J. M., Nutma, E., Philippens, I., Boszormenyi, K. P., Remarque, E. J., Bakker, J., … Middeldorp, J. (2023). Longitudinal positron emission tomography and postmortem analysis reveals widespread neuroinflammation in SARS-CoV-2 infected rhesus macaques. *Journal of Neuroinflammation*, *20*(1), 179. https://doi.org/10.1186/s12974-023-02857-z

Pfannmoller, J., & Lotze, M. (2019). Review on biomarkers in the resting-state networks of chronic pain patients. *Brain Cognition*, *131*, 4–9. https://doi.org/10.1016/j.bandc.2018.06.005

Porcaro, C., Cottone, C., Cancelli, A., Rossini, P. M., Zito, G., & Tecchio, F. (2019). Cortical neurodynamics changes mediate the efficacy of a personalized neuromodulation against multiple sclerosis fatigue. *Scientific Reports*, *9*(1), 18213. https://doi.org/10.1038/s41598-019-54595-z

https://doi.org/10.1017/S0033291723003690 Published online by Cambridge University Press

Proal, A. D., & VanElzakker, M. B. (2021). Long COVID or post-acute sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms. *Frontiers in Microbiology*, *12*, 698169. https://doi.org/10.3389/fmicb.2021.698169

Raijmakers, R., Roerink, M., Keijmel, S., Joosten, L., Netea, M., van der Meer, J., … Doorduin, J. (2022). No signs of neuroinflammation in women with chronic fatigue syndrome or Q fever fatigue syndrome using the TSPO ligand [(11)C]-PK11195. *Neurology Neuroimmunology Neuroinflammation*, *9*(1), 1–10. https://doi.org/10.1212/NXI.0000000000001113

Raijmakers, R. P. H., Jansen, A. F. M., Keijmel, S. P., Ter Horst, R., Roerink, M. E., Novakovic, B., … Bleeker-Rovers, C. P. (2019a). A possible role for mitochondrial-derived peptides humanin and MOTS-c in patients with Q fever fatigue syndrome and chronic fatigue syndrome. *Journal of Translational Medicine*, *17*(1), 157. https://doi.org/10.1186/s12967-019-1906-3

Raijmakers, R. P. H., Koeken, V., Jansen, A. F. M., Keijmel, S. P., Roerink, M. E., Joosten, L. A. B., … Bleeker-Rovers, C. P. (2019b). Cytokine profiles in patients with Q fever fatigue syndrome. *Journal of Infection*, *78*(5), 349–357. https://doi.org/10.1016/j.jinf.2019.01.006

Raijmakers, R. P. H., Roerink, M. E., Jansen, A. F. M., Keijmel, S. P., Gacesa, R., Li, Y., … Xu, C. J. (2020). Multi-omics examination of Q fever fatigue syndrome identifies similarities with chronic fatigue syndrome. *Journal of Translational Medicine*, *18*(1), 448. https://doi.org/10.1186/s12967-020-02585-5

Reeves, W. C., Lloyd, A., & Vernon, S. D. (2003). Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Services Research*, *3*, 1–9. https://doi.org/10.1186/1472-6963-3-25

Robinson, M. J., & Berridge, K. C. (2013). Instant transformation of learned repulsion into motivational "wanting". *Current Biology*, *23*(4), 282–289. https://doi.org/10.1016/j.cub.2013.01.016

Sandstrom, A., Ellerbrock, I., Lofgren, M., Altawil, R., Bileviciute-Ljungar, I., Lampa, J., … Kosek, E. (2022). Distinct aberrations in cerebral pain processing differentiating patients with fibromyalgia from patients with rheumatoid arthritis. *Pain*, *163*, 538–547. https://doi.org/10.1097/j.pain.0000000000002387

Satterthwaite, T. D., Elliott, M. A., Gerraty, R. T., Ruparel, K., Loughead, J., Calkins, M. E., … Wolf, D. H. (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage*, *64*, 240–256. https://doi.org/10.1016/j.neuroimage.2012.08.052

Shacham, S. (1983). A shortened version of the profile of mood states. *Journal of Personality Assessment*, *3*(47), 305–306. https://doi.org/10.1207/s15327752jpa4703_14

Shan, Z. Y., Barnden, L. R., Kwiatek, R. A., Bhuta, S., Hermens, D. F., & Lagopoulos, J. (2020). Neuroimaging characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A systematic review. *Journal of Translational Medicine*, *18*(1), 335. https://doi.org/10.1186/s12967-020-02506-6

Shan, Z. Y., Finegan, K., Bhuta, S., Ireland, T., Staines, D. R., Marshall-Gradisnik, S. M., & Barnden, L. R. (2018). Decreased connectivity and increased blood oxygenation level dependent complexity in the default mode network in individuals with chronic fatigue syndrome. *Brain Connectivity*, *8*(1), 33–39. https://doi.org/10.1089/brain.2017.0549

Soares, M. N., Eggelbusch, M., Naddaf, E., Gerrits, K. H. L., van der Schaaf, M., van den Borst, B., … Wust, R. C. I. (2022). Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *Journal of Cachexia Sarcopenia Muscle*, *13*(1), 11–22. https://doi.org/10.1002/jcsm.12896

Song, Y., Yao, M., Kemprecos, H., Byrne, A., Xiao, Z., Zhang, Q., … Chen, Z. S. (2021). Predictive coding models for pain perception. *Journal of Computational Neuroscience*, *49*(2), 107–127. https://doi.org/10.1007/s10827-021-00780-x

Stephan, K. E., Manjaly, Z. M., Mathys, C. D., Weber, L. A., Paliwal, S., Gard, T., … Petzschner, F. H. (2016). Allostatic self-efficacy: A metacognitive theory of dyshomeostasis-induced fatigue and depression. *Frontiers in Human Neuroscience*, *10*, 550. https://doi.org/10.3389/fnhum.2016.00550

Surian, A. A., & Baraniuk, J. N. (2020). Systemic hyperalgesia in females with gulf war illness, chronic fatigue syndrome and fibromyalgia. *Scientific Reports*, *10*(1), 5751. https://doi.org/10.1038/s41598-020-62771-9

Urchs, S., Armoza, J., Benhajali, Y., St-Aubin, J., Orban, P., & Bellec, P. (2017). MIST: A multi-resolution parcellation of functional brain networks. *MNI Open Research*, *1*, 1–18. https://doi.org/10.12688/mniopenres.12767.1

van der Schaaf, M. E., De Lange, F. P., Schmits, I. C., Geurts, D. E. M., Roelofs, K., van der Meer, J. W. M., … Knoop, H. (2017). Prefrontal structure varies as a function of pain symptoms in chronic fatigue syndrome. *Biological Psychiatry*, *81*(4), 358–365. https://doi.org/10.1016/j.biopsych.2016.07.016

van der Schaaf, M. E., Roelofs, K., de Lange, F. P., Geurts, D. E. M., van der Meer, J. W. M., Knoop, H., & Toni, I. (2018). Fatigue is associated with altered monitoring and preparation of physical effort in patients with chronic fatigue syndrome. *Biological Psychiatry Cognitive Neuroscience and Neuroimaging*, *3*(4), 392–404. https://doi.org/10.1016/j.bpsc.2018.01.015

van Der Schaaf, M. E., Schmits, I. C., Roerink, M., Geurts, D. E., Toni, I., Roelofs, K., … Knoop, H. (2015). Investigating neural mechanisms of change of cognitive behavioural therapy for chronic fatigue syndrome: A randomized controlled trial. *BMC Psychiatry*, *15*, 144. https://doi.org/10.1186/s12888-015-0515-9

VanElzakker, M. B., Brumfield, S. A., & Lara Mejia, P. S. (2018). Neuroinflammation and cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A critical review of research methods. *Frontiers in Neurology*, *9*, 1033. https://doi.org/10.3389/fneur.2018.01033

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*(5), 383–392. https://doi.org/10.1016/0022-3999(94)90099-x

Verhage, F. (1964). Intelligentie en leeftijd; onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar. *Bijdragen tot de psychologie* (Vol. *4*). Assen: Van Gorcum.

Wagner, I. C., Rutgen, M., Hummer, A., Windischberger, C., & Lamm, C. (2020). Placebo-induced pain reduction is associated with negative coupling between brain networks at rest. *Neuroimage*, *219*, 117024. https://doi.org/10.1016/j.neuroimage.2020.117024

Wang, W. E., Ho, R. L. M., Gatto, B., van der Veen, S. M., Underation, M. K., Thomas, J. S., … Coombes, S. A. (2021). Cortical dynamics of movement-evoked pain in chronic low back pain. *Journal of Physiology*, *599*(1), 289–305. https://doi.org/10.1113/JP280735

Worm-Smeitink, M., Gielissen, M., Bloot, L., van Laarhoven, H. W. M., van Engelen, B. G. M., van Riel, P., … Knoop, H. (2017). The assessment of fatigue: Psychometric qualities and norms for the checklist individual strength. *Journal of Psychosomatic Research*, *98*, 40–46. https://doi.org/10.1016/j.jpsychores.2017.05.007

Wrightson, J. G., Zewdie, E., Kuo, H. C., Millet, G. Y., & Kirton, A. (2020). Fatigue in children with perinatal stroke: Clinical and neurophysiological associations. *Developmental Medicine and Child Neurology*, *62*(2), 234–240. https://doi.org/10.1111/dmcn.14273

Zenon, A., Sidibe, M., & Olivier, E. (2015). Disrupting the supplementary motor area makes physical effort appear less effortful. *Journal of Neuroscience*, *35*(23), 8737–8744. https://doi.org/10.1523/JNEUROSCI.3789-14.2015