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Functional Neuroimaging Signatures of Fatigue in Cancer Patients: A Systematic Review Toward Neural Biomarker Identification

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Abstract

Background: Cancer-related fatigue (CRF) is a prevalent and debilitating symptom. Functional neuroimaging has emerged as a key tool to investigate its neurobiological underpinnings. A systematic synthesis is needed to map the current evidence, assess its quality, and guide future research. We aimed to

systematically review the existing literature using functional neuroimaging to investigate the neural correlates of fatigue in cancer patients, and to formally assess the quality of the included studies.

Methods: A systematic search of PubMed, Scopus, and Web of Science was conducted. Studies were included if they used functional neuroimaging to compare brain function in cancer patients with that of a control group/condition or to relate brain function to fatigue measures. Data on study characteristics, demographics, imaging parameters, and findings were extracted. The quality of individual studies was assessed using the Newcastle-Ottawa Scale (NOS), supplemented by an appraisal of neuroimaging-specific sources of bias, and each study was graded according to how directly its imaging findings were linked to fatigue (evidence tiers).

Results: Eleven reports, derived from no more than nine independent cohorts, met the inclusion criteria. Imaging modalities and analytic approaches (BOLD fMRI, ASL perfusion, fractal scaling), paradigms (resting-state, working memory, planning, verbal recall, phasic alertness) and comparison groups were heterogeneous. Three studies related imaging measures directly to fatigue within cancer patients (Tier 1), five analyzed fatigue indirectly (Tier 2), and three did not demonstrate an imaging–fatigue association (Tier 3). Tier 1 and Tier 2 evidence converged on the default mode network (DMN): fatigue was associated with greater DMN–frontal connectivity, reduced task-related DMN deactivation, and elevated posterior cingulate perfusion, whereas greater connectivity of DMN nodes with the periaqueductal gray and subgenual cingulate cortex characterized non-fatigued survivors. Lower middle frontal gyrus activity correlated with fatigue severity, and pre-treatment executive-network inefficiency predicted post-treatment fatigue. Frontoparietal hyperactivation during working-memory and planning tasks was reported mainly in comparisons defined by cancer or treatment status and was not specifically linked to fatigue. All studies

scored 7–9 on the Newcastle-Ottawa Scale, but the neuroimaging-specific appraisal identified small samples, variable motion control, and inconsistent correction for multiple comparisons.

Conclusion: Functional neuroimaging evidence specific to cancer-related fatigue is limited and heterogeneous, and several findings previously attributed to CRF reflect effects of cancer or its treatment. The most consistent fatigue-linked signal involves dysregulation of the default mode network and its coupling with frontal and brainstem regulatory regions, together with reduced frontal executive efficiency. Emerging longitudinal evidence suggests that neural inefficiency may, in some cases, precede or predict subsequent fatigue. Standardized fatigue phenotyping, analyses based on fatigue-defined contrasts within cancer populations, harmonized imaging paradigms, and adequately powered prospective designs are needed before neural biomarkers or biotypes of CRF can be established.

1. Introduction

Cancer-related fatigue (CRF) is one of the most common and distressing symptoms experienced by cancer patients, with a prevalence estimated between 70% and 100% during treatment and affecting up to one-third of survivors for years after treatment completion [1, 2]. Unlike transient tiredness, CRF is a multifactorial syndrome characterized by persistent exhaustion disproportionate to recent activity, interfering with normal functioning [3, 4]. Its profound impact on quality of life brings a critical need to understand its pathophysiology.

While peripheral mechanisms are well studied, the central nervous system (CNS) correlates remain less well understood. Functional neuroimaging, particularly functional magnetic resonance imaging (fMRI), has become an indispensable tool for investigating the neural basis of CRF. Early studies suggest CRF is associated with altered function in brain networks crucial for executive function and attention, such as the frontoparietal network (FPN) and default mode

network (DMN) [5]. However, the field is characterized by variations across paradigms, patient populations, and definitions of fatigue, making it challenging to synthesize findings [6].

An initial objective was to conduct a coordinate-based meta-analysis (e.g., Activation Likelihood Estimation, ALE). However, a preliminary survey revealed that the heterogeneity in imaging modalities (e.g., BOLD, ASL), analysis methods (e.g., activation, fractal scaling), and experimental designs was too great for a sound quantitative aggregation [7]. Therefore, this paper presents a systematic review of the functional neuroimaging literature on CRF. We aimed to systematically identify and describe all relevant studies, formally assess the quality of each included report, tabulate and summarize the principal findings, distinguish findings specific to fatigue from those attributable to cancer or its treatment more generally, and provide concrete, critical recommendations for future research.

2. Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [8, 9]. The detailed study protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) under registration identifier (CRD420261357250). The completed PRISMA 2020 checklist is provided for review in **Supplementary Table S1**.

2.1. Search Strategy

Comprehensive searches of PubMed (MEDLINE), Scopus, and Web of Science were conducted from database inception to 5 March 2026. The strategy combined controlled vocabulary (MeSH terms in PubMed) with free-text keywords for three concept blocks, which were joined with the Boolean operator

AND: (1) the population (e.g., "Neoplasms"[MeSH], cancer, tumor/tumour, neoplasm*, malignan*, oncolog*, chemotherapy, "antineoplastic agents"); (2) the exposure (e.g., "Magnetic Resonance Imaging"[MeSH], "functional magnetic resonance imaging", "functional MRI", fMRI, "resting-state fMRI", rs-fMRI, "task-based fMRI", neuroimaging); and (3) the outcome (e.g., "Fatigue"[MeSH], fatigue, "cancer-related fatigue", "cancer fatigue", CRF). Synonyms within each block were combined with OR, and field tags were adapted to each database (TITLE-ABS-KEY in Scopus; TS in Web of Science). The searches retrieved 1394 records from PubMed, 169 from Scopus, and 262 from Web of Science (1825 in total). The complete database-specific search strings, search dates, and numbers of records retrieved are provided in **Supplementary Table S2**.

2.2. Eligibility Criteria and Study Selection

Studies were included if they were original research using functional MRI to compare brain function in adult cancer patients with a control group, or to relate brain function to fatigue measures within the same subjects. Exclusion criteria were: (1) reviews or case reports; (2) purely structural MRI studies; (3) studies not measuring fatigue. Two reviewers independently screened all records, and a third expert reviewer adjudicated any disagreements. Studies in which fatigue was measured but was not the primary focus of the imaging analysis were retained, but the fatigue specificity of their findings was graded (Section 2.5).

2.3. Data Extraction

Data extraction was performed independently by two reviewers using a standardized, pre-piloted form developed a priori, with discrepancies resolved by consensus or third-author adjudication. The following domains were systematically extracted from each eligible study: (1) study characteristics, including design, and year, (2) population details, including cancer type, sample size, demographic profile of patient and comparison groups, and the validated fatigue instrument used (e.g., FACIT-F, POMS, FSI, BFI, FSS, or MFI-20), with fatigue recorded as either a continuous score or a categorical classification based on

established clinical cut-offs; (3) MRI acquisition parameters, including scanner field strength, sequence type, repetition time, echo time, voxel size, and scan duration; (4) preprocessing and analysis details, including the software platform; (5) fMRI paradigm and comparison groups, including paradigm type (task-based or resting-state), cognitive domain, and the specific experimental contrast of interest; and (6) key neuroimaging findings, including the direction of effect (hyperactivation, hypoactivation, increased or decreased connectivity, or impaired deactivation), analysis level (whole-brain, network-based, or ROI), statistical threshold and correction method, and peak MNI coordinates (x, y, z) extracted verbatim from original results tables.

2.4. Quality Assessment

2.4.1. Newcastle-Ottawa Scale (NOS)

The methodological quality and risk of bias of each included study were assessed using the Newcastle-Ottawa Scale (NOS), adapted for case-control and cohort designs. The scale assesses three domains: Selection, Comparability, and Outcome/Exposure. A study can be awarded up to 9 points, with higher scores indicating higher quality. Studies were rated as Good (7–9), Fair (4–6), or Poor (0–3).

2.4.2. Neuroimaging-Specific Risk of Bias

Because the NOS does not capture sources of bias specific to functional neuroimaging, each study was additionally appraised on five neuroimaging-specific domains, each judged as low risk, some concerns, high risk, or unclear. (N1) Sample size, based on the smallest analyzed group contributing to the principal or fatigue-related analysis: ≥30, low; 15–29, some concerns; <15, high. (N2) Head-motion and artifact control: explicit exclusion thresholds, nuisance regression of motion parameters, or artifact repair, low; realignment only or incompletely described procedures, some concerns; no information, unclear. (N3) Correction for multiple comparisons: family-wise error, false discovery rate, or an equivalent correction applied to the principal inference, low; a corrected primary test

with uncorrected exploratory follow-up, or uncorrected multivariable models, some concerns; uncorrected voxel-wise thresholds, high. (N4) Validity of the fatigue measure: a fatigue-specific instrument with an established clinical cut-off used for case definition, low; a validated fatigue-specific instrument analyzed as a continuous score, some concerns; a fatigue subscale of a broader quality-of-life or mood instrument, high. (N5) Directness of the fatigue–imaging analysis, corresponding to the evidence tier described in Section 2.5 (Tier 1, low; Tier 2, some concerns; Tier 3, high). NOS and neuroimaging-specific judgments are displayed together as a traffic-light plot (**Figure 2**). These additional domains were not specified in the registered protocol.

2.5. Fatigue Specificity of the Imaging Evidence

To determine whether each imaging finding reflected cancer-related fatigue rather than cancer or its treatment more generally, every included study was re-examined against its original report and assigned to one of three evidence tiers (**Table 2**). *Tier 1 (direct)* comprised analyses in which imaging measures were compared between fatigue-defined groups of cancer patients, or were significantly associated with fatigue severity within cancer patients only. *Tier 2 (indirect)* comprised analyses in which fatigue was explicitly modeled but the evidence was indirect, i.e., non-cancer controls were included in the fatigue model, fatigue was used to explain differences between patients and controls, or the within-patient association was inconsistent in direction or reached only trend level. *Tier 3 (contextual)* comprised studies in which imaging differences were defined by cancer or treatment status and fatigue was measured only descriptively, as a covariate, or as an eligibility criterion, without a demonstrated imaging–fatigue association. Only Tier 1 and Tier 2 evidence was used to derive the main conclusions and provisional biotypes; Tier 3 findings are reported for completeness and context.

3. Results

3.1. Study Selection and Characteristics

The search identified 1825 records. After removing duplicates, 1681 records were screened; of these, 52 were assessed for eligibility by reviewing full-text details, leading to the inclusion of 11 studies [5, 10-19]. A PRISMA flow diagram is shown in **Figure 1.** The characteristics of the included studies are summarized in **Table 1**. These 11 reports derive from no more than nine independent cohorts, because two pairs of reports share participants: Askren et al. [19] and Churchill et al. [10] analyzed the same pre-treatment breast cancer cohort, and Menning et al. [15] reported the longitudinal follow-up of the cohort described by Menning et al. [16].

Table 1. Basic Study Characteristics and Population Demographics

First Author (Year)	Cancer Type	Study Design	CRF Dx	Patients (n, Age, Sex)	Comparison (n, Age, Sex)
McDonald et al. (2012) [14]	BC	Prospective Longitudinal	FSI	Chemotherapy 16, 52.9±8.6y, 16F; No Chemotherapy 12, 52.7±7.2y, 12F	Healthy Controls: 15, 50.5±6.0y, 15F

Menning et al. (2017) [15]	BC	Prospective Longitudinal	QLQ-C30, POMS	Chemotherapy: 28, 49.4±8.8y, 28F; No Chemotherapy: 24, 51.2±6.8y, 24F	Healthy Controls: 31, 51.2±8.2y, 31F
Menning et al. (2015) [16]	BC	Cross-sectional	QLQ-C30, POMS	Chemotherapy planned: 32, 32F; No chemotherapy: 33, 52.4±7.3y, 33F	Healthy Controls: 38, 50.1±8.7y, 38F
López Zunini et al. (2013) [13]	BC	Prospective Longitudinal	POMS	Chemotherapy (pre/post): 21, 50.6±8.4y, 21F	Healthy Controls: 21, 49.7±8.8y, 21F
Hampson et al. (2015) [5]	BC	Cross-sectional	BFI (BFI ≥ 4)	Fatigued survivors: 15, 57±8y, 15F	Non-fatigued survivors: 8, 55±8y, 8F
He et al. (2025) [18]	GI Cancer	Cross-sectional	FSS	Chemotherapy: 50, 61.2±8.7y, 25M/25F	Healthy Controls: 57, 52.4±7.8y, 22M/35F
de Dreu et al. (2020) [11]	Brain Tumor (meningioma, LGG, HGG)	Cross-sectional, Correlation	MFI-20	Pre-surgical: 63 (meningioma 23, LGG 21, HGG 19); 38.7–54.5y; 29M/34F	None (within-subject correlation)

Harris et al. (2017) [12]	BC	RCT (Acupressure)	BFI (BFI ≥ 4)	Fatigued survivors: 19F (relaxing 9, 58.9±5.8y; stimulating 10, 60.1±8.6y)	Same patients six weeks before acupressure
Churchill et al. (2015) [10]	BC	Cross-sectional	FACIT-F	Pre-treatment: Chemotherapy 28F; Radiotherapy 37F	Healthy Controls: 32F
Raizen et al. (2023) [17]	BC/PCa	Prospective longitudinal	BFI	Radiotherapy: 16, 57.4y, 9M/7F	Healthy Controls: 18, 55.7±14.7y, 11M/7F
Askren et al. (2014) [19]	BC	Prospective longitudinal	FACIT-F	Chemotherapy: 28, 50±10y, 28F; No chemotherapy: 37, 53±9y, 37F	Healthy Controls: 32, 50±9y, 32F

Abbreviations: BC: Breast Cancer; BFI: Brief Fatigue Inventory; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; FSI: Fatigue Symptom Inventory; FSS: Fatigue Severity Scale; M: Male; F: Female; MFI-20: Multidimensional Fatigue Inventory-20; N: Number of subjects; POMS: Profile of Mood States; QLQ-C30: EORTC Quality of Life Questionnaire-C30; PCa: Prostate Cancer; GI Cancer: Gastrointestinal Cancer; LGG: Low Grade Glioma; HGG: High Grade Glioma; RCT: Randomized Controlled Trial.

3.2. Fatigue Specificity of the Evidence

Examination of the original reports showed that the extent to which fatigue was the focus of the imaging analysis varied across studies (**Table 2**). Three studies provided direct (Tier 1) evidence, comparing fatigued with non-fatigued survivors [5] or relating imaging measures to fatigue severity within cancer patients [11, 18]. Five studies provided indirect (Tier 2) evidence: two modeled fatigue across cancer patients and non-cancer controls [10, 19], one showed that patient–

control differences were explained by fatigue [16], one reported inconsistent within-patient associations [15], and one reported a patient–control perfusion difference with only a trend-level within-patient association with fatigue [17]. In the remaining three studies (Tier 3), imaging contrasts were defined by cancer or treatment status, and fatigue was measured descriptively, as a covariate, or as an eligibility criterion without a demonstrated association with the imaging findings [12-14].

Table 2. Fatigue specificity of the imaging analyses in the included studies

Study	Fatigue-related analysis	Participants in the fatigue analysis	Principal fatigue-related result	Evidence tier
Hampson (2015) [5]	Fatigued (BFI ≥ 4) vs. non-fatigued survivors; correlations with MFI/BFI within groups	BC survivors only (15 vs. 8)	Greater IPL–SFG and DMN–SFG connectivity in fatigued survivors, scaling with physical and mental fatigue; greater precuneus–PAG and IPL–subgenual ACC connectivity in non-fatigued survivors	Tier 1 (direct)

de Dreu (2020) [11]	Correlation of MFI-20 with phasic-alertness DMN and CEN signal change	Brain tumor patients only (n = 63)	Higher fatigue associated with reduced DMN deactivation (r = 0.47); no association with CEN activation	Tier 1 (direct)
He (2025) [18]	Correlation of FSS with regional fALFF/ReHo; depression tested as mediator	GI cancer patients only (n = 50)	Lower bilateral middle frontal gyrus fALFF associated with higher fatigue, not mediated by depression	Tier 1 (direct)
Askren (2014) [19]	Regression of post-treatment FACIT-F on pre-treatment executive-network measures	Patients and healthy controls (n = 97)	Pre-treatment executive-network spatial variance predicted post-treatment fatigue, independent of treatment group	Tier 2 (indirect)
Churchill (2015) [10]	Distress components (including FACIT-F) related to Hurst	Patients and healthy controls	Fatigue contributed to composite distress components; the main	Tier 2 (indirect)

	exponent and connectivity	(n = 97; same cohort as [19])	group effect related to anticipated treatment intensity	
Menning (2015) [16]	Patient–control imaging differences re-tested after accounting for fatigue	Patients and healthy controls	Pre-adjuvant prefrontal hyperactivation relative to controls no longer significant after accounting for fatigue	Tier 2 (indirect)
Menning (2017) [15]	Within-group correlations of BOLD change with fatigue (QLQ-C30)	Each patient group separately	Baseline fatigue ($r = 0.49$) and fatigue change ($r = -0.63$) correlated with right IPC activation change in opposite directions, in patients without systemic therapy only; no association in the chemotherapy group	Tier 2 (indirect)
Raizen (2023) [17]	PCC CBF compared with controls; correlation of CBF	Patients vs. controls (16 vs. 18); within-	PCC CBF elevated vs. controls and persisting after fatigue declined; CBF change vs. fatigue	Tier 2 (indirect)

	change with BFI change	patient correlation (n = 12)	change after a fatiguing task, rho = 0.55, p = 0.066	
McDonald (2012) [14]	Fatigue (FSI) compared descriptively between groups	Not applicable	Fatigue did not differ between groups; the authors concluded that fatigue did not account for the imaging findings	Tier 3 (contextual)
López Zunini (2013) [13]	Fatigue (POMS) entered as a covariate together with anxiety	Patients and healthy controls	Anterior cingulate hypoactivation emerged with anxiety and fatigue as covariates; fatigue modeled only as a covariate	Tier 3 (contextual)
Harris (2017) [12]	Fatigue as eligibility criterion; correlation of connectivity change with fatigue change	Fatigued BC survivors only (n = 19)	Connectivity changes differed by acupressure type but were not associated with change in fatigue	Tier 3 (contextual)

Tier 1 (direct): imaging compared between fatigue-defined groups of cancer patients, or significantly associated with fatigue within cancer patients only. Tier 2 (indirect): fatigue explicitly analyzed, but the model included non-cancer controls, fatigue explained patient–control differences, or the within-patient association was inconsistent or trend-level. Tier 3 (contextual): no imaging–fatigue association demonstrated. Abbreviations: ACC: anterior cingulate cortex;

BFI: Brief Fatigue Inventory; CBF: cerebral blood flow; CEN: central executive network; DMN: default mode network; fALFF: fractional amplitude of low-frequency fluctuations; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; FSI: Fatigue Symptom Inventory; FSS: Fatigue Severity Scale; IPC: inferior parietal cortex; IPL: inferior parietal lobule; MFI-20: Multidimensional Fatigue Inventory-20; PAG: periaqueductal gray; PCC: posterior cingulate cortex; POMS: Profile of Mood States; QLQ-C30: EORTC Quality of Life Questionnaire-C30; ReHo: regional homogeneity; SFG: superior frontal gyrus.

3.3. Quality Assessment

3.3.1. Newcastle-Ottawa Scale (NOS) Results

All studies scored 7–9 out of a possible 9 on the NOS and were rated as "Good" quality; the single randomized study was also rated "Good" within its framework (**Figure 2**). However, the NOS was not designed for neuroimaging studies and does not capture several major sources of bias in this field, including small sample size, head motion, preprocessing heterogeneity, analytic flexibility, and inconsistent correction for multiple comparisons. Uniformly "Good" NOS ratings should therefore not be interpreted as evidence of methodological robustness, and they were complemented by the neuroimaging-specific appraisal described below.

3.3.2. Neuroimaging-Specific Risk of Bias

The neuroimaging-specific appraisal was considerably less favorable (**Figure 2**). The smallest analyzed group comprised fewer than 15 participants in four studies [5, 12, 14, 17]. Motion control was limited to realignment or was incompletely described in three studies [11, 17, 19] and was rated unclear in one [13]. One study relied on uncorrected voxel-wise thresholds [14], two combined a corrected primary test with uncorrected follow-up or multivariable analyses [11, 19], and the correction method was rated unclear in two [13, 16]. Fatigue was defined using an established clinical cut-off in only two studies [5, 12], whereas

three relied on fatigue subscales of broader quality-of-life or mood instruments [13, 15, 16]. Finally, only three studies provided direct (Tier 1) fatigue-specific imaging evidence [5, 11, 18].

3.4. Imaging Acquisition and Principal Findings

MRI acquisition parameters varied across studies (**Table 3**). The majority of studies employed 3-Tesla scanners, with two exceptions: McDonald et al. (2012) and López Zunini et al. (2013) used 1.5T systems, which may have reduced signal-to-noise ratio relative to higher-field acquisitions.

Table 3. MRI Scanner and fMRI Technical/Preprocessing Details

First Author (Year)	Scanner (Field Strength, Make)	Voxel Size (mm^3)	TR (ms)	TE (ms)	Smoothing Kernel (mm)	Preprocessing Software
McDonald et al. (2012)	1.5T GE Signa LX	3.75 x 3.75 x 5.0	2500	40	8	SPM5
Menning et al. (2017)	3T Philips (Intera/Achieva)	2.3 x 2.3 x 2.3	2100	25	8	SPM8, Artrepair
Menning et al. (2015)	3T Philips (Intera/Achieva)	2.3 x 2.3 x 2.3	2100	25	8	SPM8, Artrepair
López Zunini et al. (2013)	1.5T Siemens Magnetom Symphony	NR	3000	40	10	SPM8
Hampson et al. (2015)	3T Philips Achieva	2.75 x 2.75 x 4.0	2000	30	8	SPM8, FSL, Conn, GIFT
He et al. (2025 preprint)	3T GE Discovery MR750W	3.75 x 3.75 x 5.0	3000	35	4	DPARSF

de Dreu et al. (2020)	3T Philips Achieva	3.0 x 3.0 x 3.0	2000	27.6	12	SPM12
Harris et al. (2017)	3T Philips Achieva	2.75 x 2.75 x 4.0	2000	30	8	SPM8, FSL, Conn, GIFT
Churchill et al. (2015)	3T GE Signa	3.75 x 3.75 x 5.0	1500	30	6	FSL, SPM8
Raizen et al. (2023)	3T Siemens Prisma	3.75 x 3.75 x 3.75	4000 (effective 8000)	10	8	SPM12, fMRI Grocer
Askren et al. (2014)	3T GE Signa	3.44 × 3.44 × 4.5	2000	30	8	SPM2

Abbreviations: ASL: Arterial Spin Labeling; DPARSF: Data Processing Assistant for Resting-State fMRI; fMRI: functional Magnetic Resonance Imaging; FSL: FMRIB Software Library; GIFT: Group ICA of fMRI Toolbox; mm: millimeter; ms: millisecond; T: Tesla; TE: Echo Time; TR: Repetition Time; SPM: Statistical Parametric Mapping. NR: Not Reported.

The principal neuroimaging findings are summarized in **Table 4**, and the principal fatigue-related findings are displayed in **Figure 3**. Among the Tier 1 studies, fatigued breast cancer survivors showed greater connectivity between the inferior parietal lobule and the superior frontal gyrus than non-fatigued survivors, and the strength of DMN–superior frontal gyrus connectivity scaled with mental fatigue; conversely, non-fatigued survivors showed greater connectivity of DMN nodes with the periaqueductal gray and the subgenual anterior cingulate cortex [5]. In brain tumor patients, higher fatigue was associated with reduced task-related deactivation of posterior DMN regions (lingual gyrus, cuneus, and precuneus) but not with central executive network activation [11]. In gastrointestinal cancer, lower fALFF in the bilateral middle frontal gyrus correlated with greater fatigue, independently of depressive symptoms [18]. Tier 2 evidence was directionally consistent: pre-treatment spatial variance in the executive network predicted post-treatment fatigue in a model that also included healthy controls [19]; resting perfusion of the posterior cingulate cortex was elevated in patients with CRF relative to controls, although the elevation persisted after fatigue declined and its association with change in fatigue reached only trend level [17]; pre-adjuvant prefrontal hyperactivation relative to controls was explained by fatigue [16]; parietal hyperactivation after systemic treatment co-occurred with higher fatigue at the group level, with inconsistent within-patient correlations [15]; and fractal scaling of the BOLD signal varied with composite distress components that included fatigue [10]. Studies classified as Tier 3 reported

frontoparietal hyperactivation (middle frontal gyrus, inferior parietal lobule, and precuneus) and focal hypoactivation (superior parietal lobule and anterior cingulate cortex) in comparisons defined by cancer or treatment status [13, 14], and acupressure-related modulation of insula–prefrontal and DMN–thalamic/brainstem connectivity that was not associated with change in fatigue [12]. These Tier 3 findings are consistent with compensatory recruitment but were not shown to be related to fatigue and are therefore considered contextual.

Table 4. fMRI Paradigm, Task, and Analysis Details, Graded by Evidence Tier

First Author (Year)	fMRI Paradigm	Task Details	Contrast	Anatomical Region	BA	MNI			Analysis Level	Direction of Effect	Proposed Mechanistic Interpretation	Peak Statistic (T/Z)
						x	y	z				
McDonald (2012) [Tier 3]	Task-based BOLD	N-back Working Memory	BC CTx+ > HC (baseline)	R Precuneus	7	20	-74	38	Whole-Brain	Hyperactivation	Compensatory Recruitment	T=4.03
				R Middle Frontal Gyrus	46	42	34	16				T=3.90
				R Inferior Parietal Lobule	40	46	-66	48				T=3.72
			HC > BC CTx+ (baseline)	L Superior Parietal Lobule	7	-16	-70	56	Whole-Brain	Hypoactivation	Neural Inefficiency	T=4.10
			HC > BC CTx− (baseline)	L Precuneus	7	-14	-62	56	Whole-Brain	Hypoactivation	Neural Inefficiency	T=4.07
Menning (2017) [Tier 2]	Task-based BOLD	Tower of London (Planning)	BC+SYST > BC (group × time)	L Inferior Parietal Lobule/Occipital Cortex	NR	-18	-64	36	Whole-Brain	Hyperactivation	Compensatory Recruitment	T=5.29

				R Inferior Parietal Lobule/Occipital Cortex	NR	20	-64	36				T=4.57
				L Precuneus/ Superior Parietal Cortex	NR	-2	-50	58				T=4.51
			BC < HC (group × time)	R Inferior Parietal Cortex	NR	36	-40	38	Whole-Brain	Hypoactivation	Neural Inefficiency	T=3.99
Menning (2015) [Tier 2]	Task-based BOLD	Tower of London (Planning)	BC > HC (pre-adjuvant); n.s. after adjusting for fatigue	R Dorsomedial Prefrontal Cortex	9	32	20	48	Whole-Brain	Hyperactivation	Compensatory Recruitment	T=4.18
López Zunini (2013) [Tier 3]	Task-based BOLD	Verbal Recall (Memory)	HC > BC (pre-chemotherapy)	Bilateral Anterior Cingulate Cortex	NR	- 2 2	10 4	24 28	ROI-based	Hypoactivation	Neural Inefficiency	T=3.75 T=3.48
Hampson (2015) [Tier 1]	Resting-state BOLD	Eyes open, fixation cross	Fatigued > non-fatigued BC	R Superior Frontal Gyrus	8	34	28	48	Seed-based	Increased Connectivity	DMN Dysregulation	Z=4.35
				R Inferior Parietal Lobule	39	44	-68	34				Z=4.35
				L Anterior Insula	13	-28	20	-16				Z=4.78
				R Cerebellum	N/A	52	-72	-40				Z=3.94
			Non-fatigued > fatigued BC	Periaqueductal Gray (PAG)	N/A	2	-34	-4	Seed-based	Decreased Connectivity	Loss of Protective Circuit	Z=6.61
				R Parahippocampus	35	26	-36	-12				Z=5.61

				Subgenual ACC	25	-4	16	-26				Z=4.47
				Middle Temporal Gyrus	21	40	-54	4				Z=4.43
				Primary Somatosensory	4	-48	-18	42				Z=3.72
He (2025) [Tier 1]	Resting-state BOLD	Eyes closed, awake	HC > GI Cancer (fALFF); correlates with FSS	L/R Middle Frontal Gyrus	6	-36 30	0 0	57 57	Whole-Brain	Hypoactivation	Reduced Neural Activity	T=-4.13 T=-4.35
			GI Cancer (Chemo) > HC (fALFF)	L Superior Parietal Lobule	7	-12	-78	54	Whole-Brain	Hyperactivation	Compensatory Shift	T=4.38
				R Cuneus	18	6	-69	48				T=4.87
			HC > GI Cancer (Chemo) (ReHo)	L/R Superior Frontal Gyrus	6/9	-15	39	42	Whole-Brain	Hypoactivation	Reduced Neural Synchrony	T=-4.45
de Dreu (2020) [Tier 1]	Task-based BOLD	Phasic Alertness Task	MFI-20 correlation (within patients)	L/R Lingual Gyrus, L/R Cuneus, R Precuneus	NR	NR	NR	NR	Network-based	Impaired Deactivation	DMN Dysregulation	r = 0.47, p < 0.001

Harris (2017) [Tier 3]	Resting-state BOLD	Eyes open, fixation cross	Relaxing vs. stimulating acupressure (post − pre)	Insula–L DLPFC; DMN–Pulvinar; DMN–SC/PAG	N/A	−37; −19; 13; −3	45; −31; −33; −31	21; 15; 13; −3	Network-based	Connectivity Modulation	Network Dysregulation	Z = 3.95–4.62
Churchill (2015) [Tier 2]	Task-based BOLD / Fractal Scaling	Verbal Working Memory	PRE-CHEMO > HC (Hurst exponent)	Middle Frontal Lobe; Parietal Lobe; Precuneus; Thalamus; Visual Cortex	NR	NR	NR	NR	Whole-Brain	Altered Signal Complexity	Reduced Neural Flexibility	q < 0.05 (FDR)
Raizen (2023) [Tier 2]	Resting-state ASL (Perfusion)	Psychomotor Vigilance Task	BC/PCa > HC (Hyper-perfusion, ASL)	Posterior Cingulate Cortex	23/31	N/A	N/A	N/A	ROI-based	Hyper-perfusion	DMN Hypermetabolism	p < 0.01
Askren (2014) [Tier 2]	Task-based BOLD	Verbal Working Memory Task	CTx+ > CTx− (baseline)	Frontoparietal Executive Network	N/A	N/A	N/A	N/A	Network-based	Increased Spatial Variance	Neural Inefficiency	p = 0.05
			Baseline spatial variance → post-treatment fatigue*									p = 0.002

Abbreviations: ASL: Arterial Spin Labeling; BA: Brodmann Area; BC: Breast Cancer; BC+SYST: Breast Cancer receiving systemic therapy; BOLD: Blood-Oxygen-Level-Dependent; CTx+: Chemotherapy group; CTx−: No-chemotherapy group; DLPFC: Dorsolateral Prefrontal Cortex; DMN: Default Mode Network; fALFF: fractional Amplitude of Low-Frequency Fluctuations; FDR: False Discovery Rate; fMRI: functional Magnetic Resonance Imaging; FSS: Fatigue Severity Scale; GI: Gastrointestinal; HC: Healthy Controls; L: Left; MFI-20: Multidimensional Fatigue

Inventory-20; MNI: Montreal Neurological Institute; N/A: Not Applicable; NR: Not Reported; n.s.: not significant; PCa: Prostate Cancer; R: Right; ReHo: Regional Homogeneity; ROI: Region of Interest; SC/PAG: Superior Colliculus/Periaqueductal Gray.

97 participants in total Tiers indicate the fatigue specificity of each study (see Table 2).Note: * Regression model including all three groups (28 BC chemotherapy + 37 BC no chemotherapy + 32 HC = 97 participants), with healthy controls as the reference group; pre-treatment executive-network spatial variance predicted post-treatment fatigue. Tiers indicate the fatigue specificity of each study (see Table 2). Brodmann areas are given as reported in the original studies.

4. Discussion

4.1 Principal Findings and Consistent Neural Themes

This systematic review of 11 functional neuroimaging reports reveals a neurobiological landscape of CRF that is heterogeneous and only partly fatigue-specific. When findings were graded according to how directly they related to fatigue, the fatigue-linked evidence was concentrated in the default mode network and its coupling with frontal and brainstem regulatory regions, together with reduced frontal executive efficiency, whereas the frequently reported frontoparietal hyperactivation during cognitive tasks was largely attributable to cancer or its treatment. The principal finding is therefore not a single, unitary brain biomarker of CRF, but a small body of convergent, hypothesis-generating evidence implicating dysregulation of large-scale brain networks.

4.2 Frontoparietal Network Alterations: Largely Cancer- and Treatment-Related

Task-based fMRI studies frequently reported hyperactivation of frontoparietal regions, including the middle frontal gyrus, inferior parietal lobule, and precuneus, in patients with breast cancer relative to controls, typically with preserved task performance [14-16]. This pattern is commonly interpreted as compensatory recruitment, although it may also reflect inefficient or less specialized neural processing under increased cognitive demand [20]. Critically, however, these contrasts were defined by cancer diagnosis or treatment exposure rather than by fatigue. In one prospective cohort, fatigue did not differ between groups and was not considered to account for the imaging findings [14]; in another, parietal hyperactivation after systemic treatment co-occurred with higher fatigue at the group level, but the within-patient associations were inconsistent in direction and absent in the chemotherapy group [15]; and in a third, pre-adjuvant prefrontal hyperactivation relative to controls was no longer significant after fatigue was accounted for, an analysis that necessarily combined patients and non-cancer controls [16]. Frontoparietal hyperactivation should therefore be regarded as a marker of cancer- and treatment-related cognitive burden that may overlap with CRF but has not been shown to be specific to it. The frontoparietal findings that relate more directly to fatigue point instead toward reduced efficiency: pre-treatment spatial variance in the executive network predicted later fatigue [19], and lower middle frontal gyrus activity scaled with fatigue severity within patients [18].

4.3 Default Mode Network Dysregulation

The most consistently fatigue-linked theme was dysregulation of the default mode network, observed across connectivity, activation, and perfusion measures. In breast cancer survivors grouped by fatigue status, fatigue was associated with greater connectivity between DMN nodes and the superior frontal gyrus, and the strength of DMN–superior frontal gyrus connectivity scaled with mental fatigue [5]. During a phasic-alertness task, higher fatigue in brain tumor patients was associated with reduced deactivation of posterior DMN regions, whereas central executive network activation was unrelated to fatigue [11]. Failure of the DMN to disengage during goal-directed behavior is thought to generate neural interference [21], analogous to the experience of being unable to stop one's mind from wandering during a demanding task. ASL provided complementary evidence of elevated resting cerebral blood flow in the posterior cingulate cortex, the core hub of the DMN, in patients with CRF relative to healthy controls [17]. This provides physiological evidence consistent with DMN hypermetabolism, but two caveats apply: the elevation persisted after fatigue had declined, suggesting that it may partly reflect cancer or its treatment, and its association with change in fatigue reached only trend level. Taken together, the convergence of connectivity, activation, and perfusion findings across three independent studies [5, 11, 17] makes DMN dysregulation the most consistent neural correlate of CRF in the current literature, although each of these studies was small and none has yet been replicated.

Future studies should also examine salience-network dysfunction and impaired network-switching dynamics between internally and externally directed systems. Given the likely role of salience circuitry in effort allocation, interoception, and fatigue regulation, and considering the anterior insula findings already present in the literature, salience-mediated switching between DMN and frontoparietal circuits is a critical concept in systems neuroscience that warrants further investigation.

4.4 Neurobiological Heterogeneity and Candidate CRF Biotypes

Beyond these themes, the review reveals substantial variability in the direction and localization of the reported alterations. Frontal and parietal regions showed hyperactivation in some studies and hypoactivation in others [14-16, 18]. Some studies report increased DMN connectivity with frontal regions, whereas others report reduced connectivity between the DMN and key regulatory hubs, such as the periaqueductal gray and the subgenual anterior cingulate cortex [5]. Still others identify alterations in the temporal dynamics of the BOLD signal that do not fit a simple hyper- or hypo-

activation framework [10]. Part of this variability reflects methodological heterogeneity and the inclusion of contrasts that were not fatigue-specific; part may, however, reflect genuine neurobiological heterogeneity within CRF itself [20].

This variability is not surprising when considered in the context of the clinical heterogeneity of CRF. The condition encompasses at least three distinct dimensions: physical fatigue, mental or cognitive fatigue, and motivational fatigue, and its causes are multifactorial, ranging from the direct effects of the tumor to the neurotoxic effects of chemotherapy to secondary factors such as sleep disturbance, anemia, and psychological distress [3]. It is therefore biologically implausible that a single, uniform pattern of brain dysfunction would account for all presentations of CRF. Restricting the evidence to Tier 1 and Tier 2 findings, we propose three provisional, hypothesis-generating biotypes that warrant systematic testing (**Table 5**). These are not validated subtypes: each rests on one to three small studies, and their correspondence with clinical dimensions of fatigue remains to be demonstrated.

Table 5. Provisional, Hypothesis-Generating Neurobiological Biotypes of Cancer-Related Fatigue Derived from Tier 1 and Tier 2 Evidence

Proposed Biotype	Primary Neural Signature	Predominant Symptom	Supporting Reports
DMN hyperconnectivity / impaired suppression	Increased DMN–superior frontal gyrus connectivity; reduced task-related DMN deactivation; elevated PCC perfusion	Mental fatigue; distractibility; difficulty sustaining focus	Hampson (2015) [Tier 1]; de Dreu (2020) [Tier 1]; Raizen (2023) [Tier 2]
Executive inefficiency	Reduced middle frontal gyrus spontaneous activity; high pre-treatment executive-network spatial variance	Cognitive fatigue with effortful task performance; vulnerability to post-treatment fatigue	He (2025) [Tier 1]; Askren (2014) [Tier 2]
Loss of protective regulatory coupling	Reduced connectivity of DMN nodes with the periaqueductal	Persistent physical and motivational	Hampson (2015) [Tier 1]

	gray and subgenual ACC (relative to non-fatigued survivors)	fatigue; reduced endogenous regulation	

Frontoparietal hyperactivation during cognitive tasks is not listed as a fatigue biotype because it was identified in contrasts defined by cancer or treatment status (Tier 2–3 evidence). All biotypes are hypothesis-generating and require prospective validation. Abbreviations: ACC: anterior cingulate cortex; DMN: default mode network; PCC: posterior cingulate cortex.

4.5 Implications for Treatment and Future Research

The clinical parallel to this neurobiological heterogeneity is the inconsistent efficacy of CRF treatments [22]. If the underlying brain dysfunction differs between patients, a single intervention would not be expected to be universally effective. As testable hypotheses, psychostimulants such as methylphenidate and modafinil, which broadly enhance catecholaminergic tone, might preferentially benefit patients with the executive-inefficiency profile, whereas mindfulness-based interventions, which are thought to reduce DMN-mediated rumination, might preferentially benefit those with the DMN hyperconnectivity profile. Exercise, which is known to modulate both frontoparietal and default mode networks, may benefit several profiles through different mechanisms. None of these predictions has yet been tested using neuroimaging-based stratification.

This transition parallels broader developments in precision neuroscience and psychiatry, where distributed circuit dysfunction and circuit-based biomarkers are increasingly being used to define biologically meaningful subgroups and guide individualized intervention strategies [23]. Future research must therefore shift from case-control comparisons designed to identify a single CRF biomarker to data-driven, unsupervised approaches, such as clustering algorithms applied to neuroimaging data, to identify these neurobiological subtypes within the broader CRF population. Such a precision-medicine approach, guided by functional neuroimaging, holds the promise of matching patients to the interventions most likely to correct their specific pattern of brain network dysfunction. To enable this, the field urgently requires methodological standardization: harmonized imaging paradigms, consistent fatigue assessment instruments, well-defined comparison groups, analyses based on fatigue-defined contrasts within cancer populations (for example, fatigued versus non-fatigued patients matched for treatment exposure), and prospective longitudinal designs to track the evolution of these neural signatures across the treatment trajectory. However, this pursuit must acknowledge broader

reproducibility concerns in functional neuroimaging, including the challenges of small sample sizes, multisite harmonization, analytic flexibility, and the critical need for prospective validation [24-26].

4.6 Limitations

This review has several limitations. First, the evidence base is small: only 11 reports met the inclusion criteria, and because two pairs of reports share participants, they represent no more than nine independent cohorts. Only three studies provided direct, fatigue-specific imaging evidence, and none of these findings has been replicated. Second, sample sizes were small, with fewer than 15 participants in the smallest analyzed group in four studies, which limits statistical power, inflates effect-size estimates, and reduces the reliability of brain–behavior associations. Third, the populations were clinically heterogeneous, spanning breast, prostate, gastrointestinal, and primary brain tumors and ranging from the pre-treatment period to long-term survivorship, with varied exposure to surgery, chemotherapy, radiotherapy, and endocrine therapy. Fatigue was measured with seven different instruments, some of which were subscales of broader quality-of-life or mood questionnaires, and a clinical case definition of CRF was applied in only two studies. Fourth, imaging modalities, paradigms, preprocessing pipelines, statistical thresholds, and correction methods varied, which precluded quantitative synthesis. Fifth, several analyses modeled fatigue across cancer patients and non-cancer controls and therefore cannot isolate fatigue that is specific to cancer or its treatment.

5. Conclusions

Functional neuroimaging studies of CRF remain heterogeneous, and a substantial proportion of findings previously attributed to CRF reflect effects of cancer or its treatment. When the evidence is restricted to fatigue-specific analyses, the most consistent signal involves dysregulation of the default mode network and its coupling with frontal and brainstem regulatory regions, together with reduced frontal executive efficiency. Emerging longitudinal evidence suggests that neural inefficiency may, in some cases, precede or predict subsequent fatigue. Adequately powered prospective studies using fatigue-defined contrasts within cancer populations, standardized fatigue phenotyping, and harmonized, preregistered imaging pipelines are required to establish whether these signatures can serve as biomarkers or define clinically meaningful biotypes of CRF.

Figure Legends:

Figure 1. PRISMA 2020 flow diagram of study identification, screening, and inclusion.

Figure 2. Risk-of-bias assessment (traffic-light plot).

Figure 2 Caption: Left, Newcastle-Ottawa Scale scores (Selection, maximum 4; Comparability, maximum 2; Outcome/Exposure, maximum 3) and overall rating. Right, neuroimaging-specific domains: N1, sample size; N2, head-motion and artifact control; N3, correction for multiple comparisons; N4, validity of the fatigue measure; N5, directness of the fatigue–imaging analysis (evidence tier). Bottom, proportion of studies in each judgment category for each domain**.**

Figure 3. Principal fatigue-related findings plotted at the MNI coordinates

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