Review

Neural Indicators of Fatigue in Chronic Diseases: A Systematic Review of MRI Studies

María Goñi [1],*, Neil Basu [2], Alison D. Murray [1] and **Gordon D. Waiter [1]**

[1]   Aberdeen Biomedical Imaging Centre (ABIC), Lilian Sutton Building, Foresterhill, University of Aberdeen, Aberdeen AB25 2ZN, UK; a.d.murray@abdn.ac.uk (A.M.); g.waiter@abdn.ac.uk (G.W.)
[2]   Health Science Building, Foresterhill, University of Aberdeen, Aberdeen AB25 2ZN, UK; neilbasu@abdn.ac.uk
*   Correspondence: m.goni@abdn.ac.uk; Tel.: +44-(0)-1224-438-368

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Abstract: While fatigue is prevalent in chronic diseases, the neural mechanisms underlying this symptom remain unknown. Magnetic resonance imaging (MRI) has the potential to enable us to characterize this symptom. The aim of this review was to gather and appraise the current literature on MRI studies of fatigue in chronic diseases. We systematically searched the following databases: MedLine, PsycInfo, Embase and Scopus (inception to April 2016). We selected studies according to a predefined inclusion and exclusion criteria. We assessed the quality of the studies and conducted descriptive statistical analyses. We identified 26 studies of varying design and quality. Structural and functional MRI, alongside diffusion tensor imaging (DTI) and functional connectivity (FC) studies, identified significant brain indicators of fatigue. The most common regions were the frontal lobe, parietal lobe, limbic system and basal ganglia. Longitudinal studies offered more precise and reliable analysis. Brain structures found to be related to fatigue were highly heterogeneous, not only between diseases, but also for different studies of the same disease. Given the different designs, methodologies and variable results, we conclude that there are currently no well-defined brain indicators of fatigue in chronic diseases.

Keywords: fatigue; magnetic resonance; chronic diseases

1. Introduction

The perception of fatigue is subjective, due to the interchangeable use of "tiredness" and the clinically pertinent experience of fatigue. There is no general consensus on the definition of fatigue. Nevertheless, for clinical purposes, it has been defined as an overwhelming feeling of physical and/or mental tiredness, along with a lack of energy which constrains the daily activities of the patient [1].

As opposed to weakness related to primary muscle disorders, fatigue has been conceived as a central nervous system event, considering that it remains after resting or sleeping. It may involve lack of attention, decline of executive and cognitive functions, difficulties in information processing or loss of productivity [2,3].

This symptom is often reported as one of the most burdensome, and the main cause of decrease in quality of life within chronic diseases, such as Rheumatoid Arthritis (RA) [4,5], Systemic Lupus Erythematosus (SLE) [6], primary biliary cirrhosis [7], or Human Immunodeficiency Virus (HIV) [8] among others.

There is a growing body of research that reports that aetiology of cognitive fatigue is multifactorial [9–11]. Whereas inflammation and disease activity have shown poor correlation with fatigue [12–15], variables such as pain [13,14,16–21], disability [12,16,17,21–24] and depression [13,14,25–28] among others appear to be commonly implicated in the complex process of this symptom. In summary,

fatigue is a non-precise and greatly subjective symptom, difficult to specify, and therefore, arduous to measure and study.

Due to its multidimensional nature, a substantial number of questionnaires to assess fatigue have been developed [29,30]. These questionnaires may consist of a single-item measure, multi-item measures that assess further fatigue issues and calculate an overall score, or multidimensional measures with sub-scores for several domains of fatigue (e.g., mental, physical or emotional factors). Notwithstanding the broad number of fatigue questionnaires, these are subjective measurement tools. The absence of objective biological measures and the lack of understanding of the mechanisms underlying fatigue, are the greatest obstacles in the development of therapies.

Kluger et al. [31] proposed the concept of fatigability as an objective measure of fatigue, to be distinguished from subjective fatigue, assessed through self-rated measures. This objective fatigue may be, for example, the one related to neural activity. a way to assess fatigability is to subject the patient to sustained cognitive tasks [32,33].

Structural Magnetic Resonance Imaging (sMRI) is an accurate identifier of macroscopic diseases, but is limited in its ability to identify microscopic structural alterations in the brain, which are thought to be the most relevant to fatigue [34,35]. Nevertheless, other sophisticated MRI techniques can address this gap. In particular, Diffusion Tensor Imaging (DTI) has already reported some possible neural indicators of fatigue in chronic disorders such as Multiple Sclerosis (MS) [34] and Fibromyalgia (FM) [35] among others.

Another promising technique in the search for the brain structures involved in fatigue is functional Magnetic Resonance Imaging (fMRI). Here, the performance of cognitive tasks during fMRI has demonstrated several differences between fatigue and non-fatigue populations [36–38]. Furthermore, great promise in improving the usefulness of fMRI has been shown in the study of brain activity in the resting state [39,40].

Taken together, these MRI techniques provide a tool of inestimable value in the study of the brain mechanisms involved in fatigue, with its consequent potential as an objective biomarker. In spite of this fact, few studies have employed these techniques in the field of chronic diseases. Additionally, the diversity of study designs, interventions, techniques and analytical analysis makes it difficult to compare neural correlates of fatigue and hence, to confirm if the neurophysiology of fatigue is something generic or specific for each disease.

This systematic review (SR) aims to summarize those MRI studies applied in the search of neural indicators of fatigue in chronic diseases. Our main goals are: (1) to determine if there are well-defined neural indicators of fatigue in chronic diseases; (2) to determine if there are common fatigue indicators across chronic diseases; and given the variety of interventions and designs; (3) to determine which is the best approach to follow in the search of neural indicators of fatigue.

2. Methods

To ensure high quality reporting, the current systematic review adheres to the recommendation for systematic reviews of the PRISMA statement [41]. The literature search was based on a predefined list of search terms, inclusion, exclusion and quality criteria. The approaches used for data collection, extraction of characteristics and analysis of results are fully described.

2.1. Information Sources

A comprehensive search strategy was developed for studying fatigue within chronic diseases through neuroimaging techniques. Experimental and observational studies, with prospective or retrospective data collection, cross-sectional and longitudinal design, cohort-, case control- and randomized-designed studies were included in this review.

The review was carried out by searching electronic databases and through consultation with experts in the field and a medical librarian specialist. Studies were identified through Medline (Ovid Medline (R)

1946 to 22 April 2016), Embase (1974 to 27 April 2016), PsycInfo (1806 to 22 April 2016) and Scopus. All studies were included, without any language or date restriction. The last search was run on 28 April 2016.

2.2. Search

The following search terms were used for all databases: (fatigue OR lethargy OR weakness OR weariness OR debility OR enervation OR exhaustion OR faintness OR feebleness OR heaviness OR languor OR lassitude OR listlessness OR burnout OR fatigation OR tiredness OR overtired* OR asthenia) [title] AND ("magnetic resonance" OR MRI OR fMRI OR neuroimaging OR "diffusion tensor imaging" OR "voxel-based morphometry" OR "voxel based morphometry") [title/abstract] AND (brain OR cerebr* OR neur*) [title/abstract] NOT ("multiple sclerosis" OR MS) [title].

2.3. Study Selection

In the search of neural changes related to fatigue, the SR was focused on the study of mental or cognitive fatigue, discarding physical fatigue due to muscular disorders. The non-invasive and non-ionizing nature, high resolution, great contrast between tissues and ability to detect subtle changes, makes the MRI one of the favourite tools in current clinical and research practice [42]. This SR focuses on MRI studies, excluding other neuroimaging techniques such as Computed Tomography (CT) or Positron Emission Tomography (PET). Another fact to take into account is that primary central nervous system (CNS) diseases generally induce gross structural abnormalities on MRI. Such abnormalities may mask some of the more subtle neural correlates (measured by more advanced MR protocols), which are expected to provide insight in the context of fatigue. Therefore, CNS diseases such as Parkinson's disease, post-stroke syndrome, multiple sclerosis or amyotrophic lateral sclerosis among others were excluded.

As opposed to epidemiological studies, most of the neuroimaging studies make use of small sample sizes. However, good statistical power can still be achieved with sample sizes between 10–15 subjects [43,44]. In this review, studies with a minimum of 10 subjects were included.

Therefore, studies were included if they met the following criteria: (1) observational or interventional study design; (2) investigation of mental or cognitive fatigue; (3) application of structural or functional magnetic resonance imaging and (4) study of chronic disease. Studies were excluded if they: (1) study muscular or physical fatigue; (2) use non MR techniques (i.e., Positron Emission Tomography (PET), Computed Tomography (CT), etc.); (3) study primary CNS diseases (as Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), stroke, etc.); (4) had sample sizes with less than 10 participants and (5) were single cases. After deletion of duplicates, the titles and abstracts of all records were reviewed.

2.4. Data Extraction

The specific outcomes extracted from each study included: (1) disease; (2) demographic characteristics of patients (number, male/female, age mean and standard deviation); (3) demographic characteristics of control group (number, male/female, age mean and standard deviation); (4) study design (cross-sectional or longitudinal); (5) period of follow-up (if applicable); (6) task during fMRI (if applicable); (7) method of assessment of fatigue; (8) imaging modality and (9) statistical approach.

2.5. Synthesis of Results

Brain correlates of fatigue were extracted for each of the studies. The outcomes were analysed according to: (1) illness and (2) neuroimaging techniques. Fatigue inducing tasks were reported for functional neuroimaging studies.

2.6. Quality Assessment

Those studies accomplishing the inclusion and exclusion criteria were evaluated for quality assessment using an established 10-item quality score [45]. The list of questions are: (1) Does the study have a clearly defined research objective? (2) Does the study adequately describe the inclusion criteria? (3) Does

the study adequately describe the exclusion criteria? (4) Does the study report on the population parameters/demographics? (5) Does the study report details on assessment of fatigue? (6) Does the study provide details of imaging protocol? (7) Does the study provide a proper control group? (8) Does the study apply proper statistical analysis? Correction for multiple comparisons? (9) Does the study adequately report on the strength of the results? and (10) Do the authors report on the limitations of their study?

3. Results

3.1. Study Selection

The search of Medline, Embase, PsycInfo and Scopus databases provided a total of 1202 citations. After deleting duplicates, 727 papers remained. Of these, a total of 655 studies were discarded after reviewing titles and abstract, as they did not meet the inclusion or exclusion criteria. Two hundred and forty-seven were discarded for reporting single cases. Ninety-five of the studies were reviews, book chapters, did not have an abstract or were theoretical reports. a further 169 studies were excluded for being focused on muscular or physical fatigue. From the remaining papers, 38 more were discarded, as they studied fatigue in healthy participants only, and another 59 studies because they investigated non related illnesses (brain cancer, ALS, MS, infarction, stroke, clinically isolated syndrome, stress-related exhaustion, cocaine addiction or scleroderma). Twenty-two more studies were excluded for not studying fatigue, 7 for not using neuroimaging techniques, 17 more for using non related imaging techniques (PET, CT, etc.), and 1 because it focused on animal models. Finally, 72 remaining papers which met the inclusion and exclusion criteria were selected for full-text reading.

After reading the full papers, 46 studies were discarded. From them, 29 were meeting abstracts or posters or it was not possible to access the full text [46–74]. Another 6 of the papers used a very small number of patients [36,75–79], 6 of them did not fully define fatigue [80–85], 1 was a protocol [86], 1 a mini review [87], 2 of them employed non related imaging techniques [88,89] and another one studied physical fatigue [90].

Finally, 26 studies remained [39,40,91–114]. Figure 1 shows the process followed in this review.
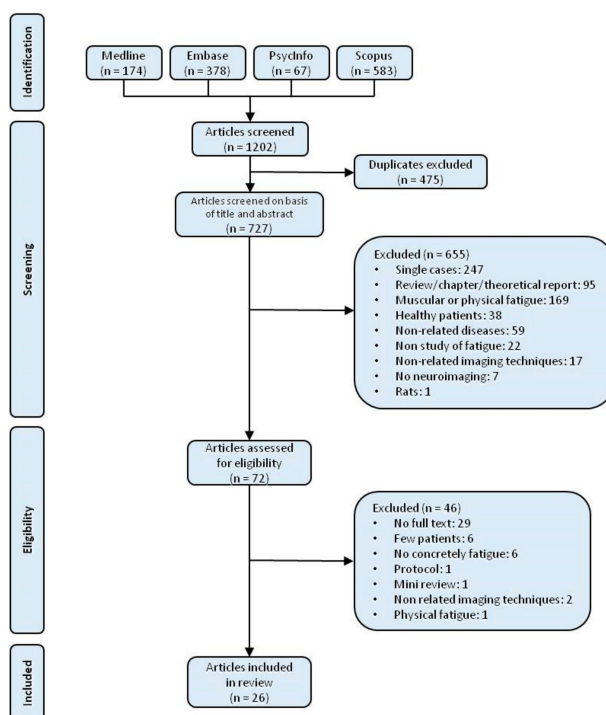

Figure 1. Flowchart of the review procedure.

3.2. Study Details and Characteristics

Table 1 summarizes the study characteristics pertinent to our research: demographic features, study design, duration of follow-up, task during the fMRI, fatigue assessment, imaging modality and statistic methods.

Table 1. Characteristics of included studies.

Ref.	Disease	User Group			Control Group			Design	Follow-Up	Task	Fatigue Assessment	Modality	Statistical Method
		n	Male/Female	Age Mean (std)	n	Male/Female	Age Mean (std)						
[93]	AS	129 TNF-treated	95/34	43.6 (11.4)	NA	NA	NA	Cross-sectional	NA	NA	FSS	NA	Pearson test, Student *t* test, paired *t* test, Wilcoxon signed-rank test, Spearman's rank order correlation, forward stepwise selection in multivariate GLM
		14	11/3	37.6 (11.9)	14	11/3	37.2 (10.2)	Longitu-dinal	At baseline and 4 months after the start of TNF treatment	NA	FSS	sMRI	
[97]	AS	20	15/5	34.8 (11.9)	20	15/5	34.9 (9.6)	Cross-sectional	NA	NA	FSS	sMRI, DTI	MonteCarlo simulations, Spearman's correlation, multiple stepwise regression analysis
[98]	Cancer	32 and 33 BC scheduled and not indicated to receive ChT	0/32 0/33	50.2 (9.2) (Pre-ChT+) 52.4 (7.3) (Pre-ChT-)	38	0/38	50.1 (8.7)	Cross-sectional	NA	ToL, Paired Associates Memory Task	CFS	sMRI, FLAIR, 1H-MRS, PRESS, DTI, fMRI	ANOVA, Chi-squared test, z-scores, Mahalanobis Distance, logistic regression, variance-covariance matrix
[99]	Cancer	28 and 37 treated with and without ChT	0/28 0/37	50.0 (10) (ChT) 53.0 (9) (No ChT)	32	0/32	50.0 (9)	Longitu-dinal	1 month post-ChT (aprox. 5 months between scans)	VWMT	FACIT-F	fMRI	Multiple linear regression analysis, *t* tests, ANOVA, Pearson correlation
[100]	Cancer	20 fatigued cancer survivors	10/10	47.9 (10.1)	20 non fatigue cancer survivors	10/10	48.9 (9.7)	Cross-sectional	NA	NA	CIS-fatigue	NA	Shapiro-Wilk test, Chi square tests, independent samples *t* tests, Mann-Whitney U tests, Wilcoxon matched-pairs tests
		25 fatigued cancer survivors (selected for intervention)	14/11	48.8 (9.4)	14 fatigued cancer survivors (selected for waiting list)	5/9	50.6 (10.9)	Longitu-dinal	At baseline and 6 months later	CBT (for the user group)		sMRI, 1H-MRS	
[101]	PBC	14 PBC (stage I–II disease) 4 PBC (stage III–IV)	0/14 0/4	60.0 (–) (41–76) [a] 48.0 (–) (39–59) [a]	11 HC	0/11	47 (–) (38–65) [a]	Cross-sectional	NA	NA	FIS	sMRI, 1H-MRS, MTR	Shapiro-Wilk test, Student's *t* test, Mann-Whitney U test, Pearson's correlation
[96]	GPA	12 fatigued 16 non fatigued	6/6 6/8	58.5 (15.9) (fatigued) 51.6 (13.8) (non fatigued)	13 general popula-tion with idio-pathic fatigue	7/6	52.2 (10.5)	Cross-sectional	NA	PASAT	CFS	sMRI, fMRI	Fisher's exact tests, *t* tests, Mann-Whitney tests, MonteCarlo simulations
[102]	GPA	14 GPA with chronic fatigue	6/8	58.6 (15.1)	14 GPA without fatigue	6/8	51.6 (13.8)	Cross-sectional	NA	NA	CFS	sMRI, DTI, FLAIR	Mann-Whitney tests, *t* tests, x^2 tests
[103]	Gulf War Illness	31	11/9	45.9 (–) (43.2–48.4) [a]	20	25.6	45.6 (–) (41.2–50.5) [a]	Cross-sectional	NA	NA	Ordinal fatigue rating, CFS, MFI, SF-36	DTI	Student's *t* test, Fisher's exact tests, *p* values, Bonferroni corrections, ROC, Pearson's function, Spearman's function, stepwise multivariate linear regression analysis
[104]	Hepatitis C	23 initiation IFN-α treatment (19 completed both MRI scans, and 20 both blood samples)	17/6	48.8 (10.9)	NA	NA	NA	Longitu-dinal	qMT and blood sampling at baseline and 4 h after IFN-α injection. Behavioural and psychological assessments at both scanning sessions and at treatment weeks 4, 8, 12 and 24	NA	VAS-f	sMRI, qMT	ANOVA, paired sample *t*-tests, regression analysis, Mauchly's sphericity test, Levenberg-Marquardt nonlinear least squares, FEW

Table 1. *Cont.*

Ref.	Disease	User Group			Control Group			Design	Follow-Up	Task	Fatigue Assessment	Modality	Statistical Method
		n	Male/Female	Age Mean (std)	*n*	Male/Female	Age Mean (std)						
[105]	HIV	82 fatigued HIV patients	71/11	44.0 (41–50) [b]	46 non-fatigued HIV patients	41/5	48.0 (43–54) [b]	Longitu-dinal	At baseline, and weeks 12 and 24 (Just 62 of the 128 patients underwent 1H-MRS)	NA	FSS	MRS	Kuskal-Wallis tests, Score tests, GEE models
[95]	PPS	42 PPS 49 MS	15/27 (PPS) 17/32 (MS)	60.86 (7.65) (PPS) 46.18 (9.4) (MS)	27	11/16	46.96 (14.58)	Cross-sectional	NA	NA	FSS	sMRI	Multivariate linear regression, Spearman correlation, unpaired *t*-test
[92]	PPS	22	–	–	NA	NA	NA	Cross-sectional	NA	NA	Postpolio fatigue questionnaire	sMRI	Produce moment correlations, linear regression, independent *t* tests
[39]	CFS	17 ME/CFS	0/17	49.82 (11.78)	17 HC	0/17	48.88 (12)	Cross-sectional	NA	NA	FFQ, VAS	sMRI, pCASL FC	Spearman's rho
[40]	CFS	19 ME/CFS	0/19	52.33 (10.63)	17 HC	0/17	48.75 (11.75)	Cross-sectional	NA	NA	MFI	sMRI, ASL FC, BOLD FC	*t*-tests, ICA, Pearson
[106]	CFS	18	0/18	43.9 (4.8)	18 HC	0/18	45.9 (3.2)	Cross-sectional	NA	6 min passive-viewing block scan	CFS	sMRI, fMRI, FC	Fisher, independent *t*-tests, ANOVA
[107]	CFS	15	7/8	46.5 (13.2)	14	6/8	46.6 (14.6)	Cross-sectional	NA	NA	MFI-20	sMRI, DTI, ASL	Pearson correlation, *t* tests, ROC curve
[108]	CFS	18	2/16	44.2 (11.1)	41 HC	8/33	47.2 (9.2)	Cross-sectional	NA	Gambling	MFI-20, SF-36	sMRI, fMRI	*t*-test, Chi-square test, Fisher exact test, Welch *t*-test, MANCOVA, Bravais-Pearson correlation
[109]	CFS	25	6/19	31.7 (8.8)	25 HC	6/19	33.7 (10.3)	Cross-sectional	NA	NA	CFS fatigue duration	sMRI	Regressions, Bonferroni corrected *p* values
[110]	CFS	12	4/8	33.75 (7.64)	11 HC	4/7	34.36 (6.77)	Cross-sectional	NA	Fatigue and anxiety provocation task	CFS, PF-SF36	sMRI, fMRI	Student's *t* tests, x^2, ANOVA
[91]	CFS	22	0/22	36.6 (2.5)	22 HC	0/22	37.1 (2.2)	Longitu-dinal	Before and after CBT (6–9 months)	NA	Physical assessment (actometer), perceived fatigue severity (checklist individual strength)	sMRI	Tailed multivariate linear regression analysis, *t*-tests, family-wise error correction, Spearman's correlation, Mahalanobis distance to check for multivariate outliers
[111]	CFS	17	7/10	35.53 (6.17)	12 HC	4/8	33.5 (7.12)	Cross-sectional	NA	n-Back task	PF-SF36, CFS	sMRI, fMRI	Student *t* test, x^2, Mann-Whitney U tests, Wilcoxon test

Table 1. *Cont.*

Ref.	Disease	User Group			Control Group			Design	Follow-Up	Task	Fatigue Assessment	Modality	Statistical Method
		n	Male/Female	Age Mean (std)	*n*	Male/Female	Age Mean (std)						
[112]	CFS	6 CFS with verbal working memory difficulties according to PASAT	0/6	38.17 (9)	7	3/4	30.71 (9.6)	Cross-sectional	(scan) Baseline → task1 → task2 → task1 → task2	Auditory monitoring test,	Neuropsychological testing	sMRI,	Student *t* test, analysis of covariance
		19 CFS without verbal memory difficulties	3/16	37.53 (8)	15	5/10	30.80 (7.5)	Cross-sectional	(scan) Baseline → task1 → task2 → task1 → task2 (STAI) before and after scanner	mPASAT, BDI, STAI	Neropsychological testing MFI-20	fMRI	
[94]	CFS	16	10/6	34.0 (-)	49 HC	27/22	34.44 (–)	Cross-sectional	NA	NA	Self-reported ratings based on daily activities	sMRI	Permutation tests, Spearman's rank correlation coefficient
[113]	CFS	16	0/16	28.4 (6)	16 HC	0/16	24.9 (6.4)	Cross-sectional	NA	Motor and visual imagery task	CIS-R, mean actometer score	sMRI, fMRI	GLM, regressions MANOVA, ANCOVA
[114]	CFS	15 without depression 11 with depression	7/8 1/10	28.4 (–) (25.5–31.3) [a] 31.3 (–) (27.7–34.8) [a]	18 HC	3/15	32.9 (–) (29.3–36.5) [a]	Longitu-dinal	Cognitive testing at baseline and 3–6 months later (just for 14 subjects)	NA	fatigue questionnaire	sMRI	ANOVA, multiple linear regression analysis

ANOVA: Analysis of Variance; AS: Ankylosing Spondylitis; ASL: Arterial Spin Labelling; BC: breast cancer; BOLD: Blood Oxygen Level Dependent; CBT: Cognitive Behaviour Therapy; CFS: Chronic Fatigue Syndrome or Chalder Fatigue Scale; ChT: chemotherapy; CIS: Checklist Individual Strength; DTI: Diffusion Tensor Imaging; FACIT-F: Functional Assessment of Chronic Illness Therapy—fatigue; FC: functional connectivity; FEW: Family Wise Error; FFQ: Florida Fatigue Questionnaire; FIS: Fatigue Impact Scale; FLAIR: Fluid-attenuated inversion recovery; fMRI: functional Magnetic Resonance Imaging; FSS: Fatigue Severity Scale; GEE: Generalized Estimating Equations; GLM: General Linear Modelling; GPA: Granulomatosis with Poliangiitis; HC: Healthy Control; HIV: Human Immunodeficiency Virus; ICA: Independent Component Analysis; IFN-α: Interferon—α; MANCOVA: Multivariate Analysis of Variance; MFI: Multidimensional Fatigue Inventory; MRS: Magnetic Resonance Spectroscopy; MS: Multiple Sclerosis; MTR: Magnetization Transfer Ratio; NA: Not applicable; PASAT: Paced Auditory Serial Attention Task; PBC: Primary Biliary Cirrhosis; pCASL: pseudo-Continuous Arterial Spin Labelling; PF-SF36: Physical Functioning scale from the 36-item Short Form Health Survey; PPS: Postpoliomyelitis syndrome; PRESS: Point Resolved Spectroscopy; qMT: quantitative Magnetization Transfer; ROC: Receiver Operating Characteristic; SF-36: Short Form 36; sMRI: structural Magnetic Resonance Imaging; STAI: State and Trait Anxiety Inventory; TNF: Tumor Necrosis Factor; ToL: Tower of London; VAS-f: Visual Analogue Scale—fatigue; VWMT: Verbal Working Memory Task. [a] Mean plus range; [b] Median plus IQR.

3.3. Quality Assessment

All 26 studies were assessed for quality (Table 2). Nineteen studies [39,40,91,93,95–98,100,101,103, 106–108,110–114] were of high quality, as they met all the quality criteria. Four studies [99,102,104,109] were of very good quality and two of good quality [92,94]. One study [105] was judged to be of fair quality, because it had incomplete inclusion/exclusion criteria, lacked details of the imaging protocol, statistical assessment and did not have an analysis of the limitations of the study.

Table 2. Quality assessment of included studies.

| Reference | Year | Pathology | Design | Scoring Criteria for Quality Assessment | | | | | | | | | | Score |
				1	2	3	4	5	6	7	8	9	10	(%)
[93]	2015	AS	Cross-sectional Longitudinal	Y	Y	Y	Y	Y	Y	N Y	Y	Y	N	100
[97]	2014	AS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[98]	2015	Cancer	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[99]	2014	Cancer	Longitudinal	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	90
[100]	2013	Cancer	Cross-sectional Longitudinal	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[101]	2004	PBC	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[96]	2014	GPA	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[102]	2013	GPA	Cross-sectional	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	90
[103]	2013	Gulf War Illness	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[104]	2016	Hepatitis C	Longitudinal	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	90
[105]	2010	HIV	Longitudinal	Y	N	N	Y	Y	N	Y	N	Y	N	50
[95]	2014	PPS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[92]	1994	PPS	Cross-sectional	Y	Y	Y	N	Y	Y	N	Y	Y	Y	80
[39]	2016	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[40]	2016	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[106]	2015	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[107]	2015	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[108]	2014	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[109]	2011	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	90
[110]	2008	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[91]	2008	CFS	Longitudinal	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[111]	2006	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[112]	2005	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[94]	2004	CFS	Cross-sectional	Y	Y	N	Y	Y	Y	Y	Y	Y	N	80
[113]	2004	CFS	Cross-sectional	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
[114]	1995	CFS	Longitudinal	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100

Assessment criteria questions: (1) Does the study have a clearly defined research objective? (2) Does the study adequately describe the inclusion criteria? (3) Does the study adequately describe the exclusion criteria? (4) Does the study report on the population parameters/demographics? (5) Does the study report details on assessment of pain? (6) Does the study provide details of imaging protocol? (7) Does the study provide a proper control group? (8) Does the study apply proper statistical analysis? Correction for multiple comparisons? (9) Does the study adequately report on the strength of the results (e.g., ways of calculating effect sizes, reporting of confidence intervals/standard deviation)? (10) Do the authors report on the limitations of their study? Y = yes, N = no, Y/N = applies partially; AS: Ankylosing Spondylitis; CFS: Chronic Fatigue Syndrome; GPA; Granulomatosis with Poliangiitis; HIV: Human Immunodeficiency Virus; PBC: Primary Biliary Cirrhosis; PPS: Pospoliomyelitis Syndrome.

3.4. Synthesis of Results

Brain correlates of fatigue were extracted for each of the studies, and they are summarized in Table 3.

Table 3. Results of brain indicators of fatigue for each study.

Reference	Pathology	Summary of Key Neuroimaging Findings Related to Fatigue	Quality Score (/10)
[93]	AS	Negative correlation between fatigue reduction after anti TNF-α therapy and cortical thickness of the insula, primary sensory cortex/inferior parietal sulcus and superior temporal polysensory areas.	100
[97]	AS	Negative correlation between fatigue scores and amount of GM in areas of the dorsal and ventral attention networks, the somatosensory cortices, and the caudate nucleus. Positive correlation between fatigue scores and GM within the executive control network and putamen.	100
[98]	Cancer	Positive correlation between fatigue and ToL task BOLD activation across groups in the dorsomedial prefrontal cortex.	100
[99]	Cancer	Prediction of post-treatment fatigue severity by pre-treatment spatial variance in executive network activation.	90
[100]	Cancer	No significant findings.	100
[101]	PBC	Positive correlation between fatigue score and blood manganese and copper concentrations. Significant reduction in globus pallidus/WM and globus pallidus/PU MTR indices in the high fatigue group compared with the low fatigue group, in stage I–II patients.	100
[96]	GPA	$\uparrow$ activation in the right thalamus, left paracentral lobule, left medial frontal gyrus and right medial globus pallidus among GPA cases compared with GPA controls.	100
[102]	GPA	$\uparrow$ structural integrity in fornix and cingulum among GPA cases.	90
[103]	Gulf War Illness	Positive correlation of fatigue, pain, and $\uparrow$ axial diffusivity with the right inferior fronto-occipital fasciculus.	100
[104]	Hepatitis C	Correlations bilaterally between shifts in kf and T2f within the ventral striatum and the subsequent development of fatigue.	90
[105]	HIV	$\downarrow$ levels of the cellular energy marker total creatine in the basal ganglia within fatigued participants.	50
[95]	PPS	No significant findings.	100
[92]	PPS	Small discrete or multiple punctate areas of hyperintense signal (HS) in the reticular formation, putamen, medial leminiscus or WM tracts imaged in 55% of the subjects reporting $\uparrow$ fatigue and none in those reporting $\downarrow$ fatigue.	80
[39]	CFS	Negative correlation between fatigue ratings and connectivity between left parahippocampal gyrus connectivity and left postcentral gyrus and left supra-marginal gyrus. Positive correlation between fatigue and connectivity of anterior cingulate cortex withthe posterior cingulate cortex, left thalamus, and left hippocampus.	100
[40]	CFS	Negative correlation between fatigue and fC between salience network and posterior cingulate cortex. Negative correlation between fatigue and fC between resting state network and anterior midcingulate cortex.	100
[106]	CFS	Positive correlation between fatigue and connectivity between posterior cingulate cortex and dorsal anterior cingulate cortex.	100
[107]	CFS	No significant findings.	100
[108]	CFS	Negative correlation between fatigue and activation in the right globus pallidus.	100
[109]	CFS	Negative correlation between fatigue duration and WM volume in the midbrain.	90

Table 3. *Cont.*

Reference	Pathology	Summary of Key Neuroimaging Findings Related to Fatigue	Quality Score (/10)
[110]	CFS	During provocation of fatigue, ↑ activation in the occipito-parietal cortex, posterior cingulate gyrus and parahippocampal gyrus, and ↓ activation in dorsolateral and dorsomedial prefrontal cortices in CFS compared to controls.	100
[91]	CFS	Significant ↑ in GM volume, localized in the lateral prefrontal cortex in CFS cases, with CBT.	100
[111]	CFS	During 1-back condition, ↑ activation in medial prefrontal regions, including the anterior cingulate gyrus, in CFS cases compared to control subjects. On more challenging conditions, ↓ activation in dorsolateral prefrontal and parietal cortices in CFS cases. On the 2- and 3-back conditions, significant activation of a large cluster in the right inferior/medial temporal cortex in CFS cases.	100
[112]	CFS	Positive correlation between fatigue and BOLD signal change in the left superior parietal region, bilateral supplemental and premotor regions.	100
[94]	CFS	Negative correlation between fatigue and right dorsolateral prefrontal-cortex.	80
[113]	CFS	No significant findings	100
[114]	CFS	White-matter lesions in a minority from all groups.	100

AS: Ankylosing Spondylitis; BOLD: Blood Oxygen Level Dependent; CBT: Cognitive Behavioural Therapy; CFS: Chronic Fatigue Syndrome; FC: functional connectivity; GM: Grey Matter; GPA; Granulomatosis with Poliangiitis; HIV: Human Immunodeficiency Virus; MFI: Multidimensional Fatigue Inventory; MTR: Magnetization Transfer Ratio; PBC: Primary Biliary Cirrhosis; PPS: Pospoliomyelitis Syndrome; TOL: Tower of London; WM: White Matter.

From a total of 26 studies, seven of the studies adopted a longitudinal approach, while the remaining ones were cross-sectional (Figure 2).
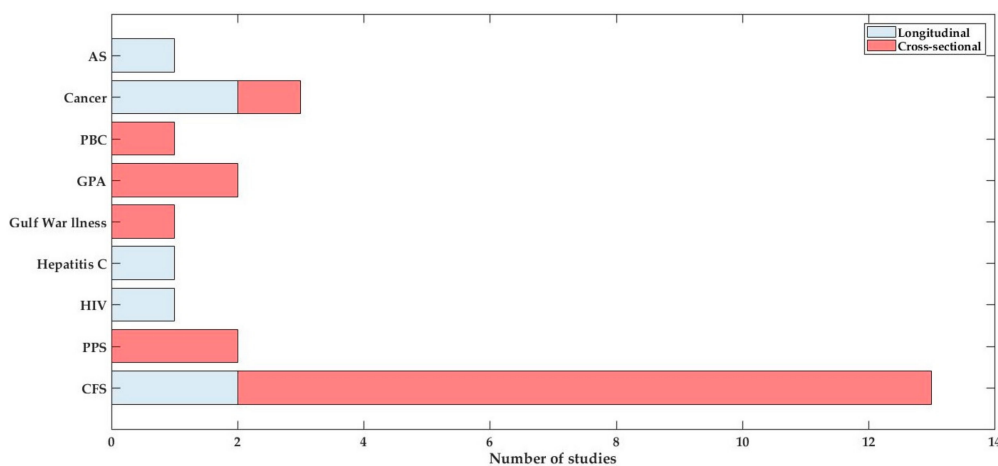
Figure 2. Distribution of longitudinal and cross-sectional studies per disease.

Next, the results are explained:

(a) Disease type

Neural correlates of fatigue in ankylosing spondylitis were mainly found in the parietal lobe, specifically in the inferior parietal sulcus [93] and postcentral gyrus [93,97], and the basal ganglia (caudate nucleus and putamen [97]). Other regions such as superior temporal polysensory area and insula were correlated with fatigue reduction after anti TNF-α therapy. Fatigue scores [97] were negatively correlated with GM volume in the dorsal and ventral attention networks, and positively

correlated in the executive control network. In the case of granulomatosis with polyangiitis (GPA) [96], higher activation during a fatigue task in the medial frontal gyrus, paracentral lobule, globus pallidus and thalamus was found, while Basu et al. suggested fornix and cingulum play an important role in GPA-related fatigue [102]. With regard to chronic fatigue syndrome (CFS), results between studies were heterogeneous. Most of the significant correlates of fatigue were found in the frontal lobe (dorsolateral prefrontal cortex [94,110], dorsomedial prefrontal cortex [110], medial prefrontal cortex [111], lateral prefrontal cortex [91], medial superior frontal gyrus [106], and bilateral supplemental and premotor region [112]) and the limbic system (parahippocampal gyrus [39,110], anterior cingulate [39,40,106,111], posterior cingulate [39,40,110], and thalamus and hippocampus [39]). Other areas related to fatigue were found in the parietal lobe (supramarginal gyrus and postcentral gyrus [39], and superior parietal region [112]), midbrain [109] and globus pallidus [108]. Cope et al. found white matter lesions in a minority of all groups [114], while Zeineh et al. and De Lange et al. reported no significant findings [107,113]. Studies in other diseases reported varying results. Regarding cancer, dorsomedial prefrontal cortex [98] and executive network [99] were found to be related with fatigue. In [100] no significant findings were reported. Other correlates with cognitive fatigue were found in globus pallidus in the case of cirrhosis [101], ventral striatum in Hepatitis C [104] and inferior fronto-occipital fasciculus in Gulf War Illness [103], whereas in postpoliomyelitis (PPS), putamen, reticular formation and medial leminiscus was related with fatigue [92], while Trojan et al. did not find significant results [95]. Finally, basal ganglia was related to fatigue in HIV patients [105], although the quality of this study was judged to be only fair.

(b) Neuroimaging technique

FMRI was employed in nine of the studies: cancer [98,99], GPA [96] and CFS [106,108,110–113]. DTI was carried out in 5 of the studies: AS [97], cancer [98], GPA [102], Gulf War Illness [103] and CFS [107]. Functional connectivity was assessed in CFS [39,40,106]. MRS was employed in cancer [98,100], cirrhosis [101] and HIV [105]. Other techniques such as qMT were used in Hepatitis C [104] and MTR in cirrhosis [101]. The different fatigue-induced approaches during the fMRI included the Tower of London task [98], Paired Associates Memory Task [98], verbal working memory task [99], Paced Auditory Serial Attention Test (PASAT) [96,112], gambling [108], n-Back task [111] and a motor and visual imagery task [113].

4. Discussion

4.1. Summary of Evidence

In the present article, we have systematically reviewed the available MRI studies in chronic diseases where fatigue is a common burden. In the case of ankylosing spondylitis (AS), a form of arthritis, fatigue is considered as a significant symptom [21,115]. This symptom is so prevalent in AS that it has been suggested to be considered as an independent domain from other symptoms related to the disease, such as pain or impairment [116]. This review compiled two AS studies reporting fatigue-related structures [93,97]. Some of these structures, such as insula, dorsal and ventral attention network and the executive control network are related to cognitive functions, while other structures such as the primary sensory cortex, inferior parietal sulcus and superior temporal polysensory area are involved in sensory experience. Cancer-related fatigue is the most prevalent and debilitating symptom reported by patients [117]. Approximately 90% of patients treated with radiation and 80% of patients treated with chemotherapy suffer from fatigue [118]. In this review, we gathered three studies regarding cancer-related fatigue, although just two of them, relating to breast cancer, stated significant findings. Blesch et al. reported that 99% of breast cancer patients experienced some level of fatigue [119]. Dorsomedial prefrontal cortex and the executive network were found to be related to fatigue, being both structures involved in cognitive functions. With regard to primary biliary cirrhosis, a long-term liver disease, long term fatigue affects approximately 68–85% of the patients [7,120], considered as the worst or one of the worst symptoms in around half of them [120]. Only one paper

studying fatigue correlates in PBC accomplished the inclusion criteria of this review. This paper reported the globus pallidus structure, associated with the regulation of voluntary movement, to be related with fatigue. Granulomatosis with Poliangiitis (GPA) is a rare multisystem autoimmune disorder of undetermined etiology. Although fatigue prevalence in GPA has not been reported, studies within other rheumatic disorders exhibited rates between 60% and 90% [121–123]. In this review, two studies regarding the GPA-related fatigue were presented. Basu et al. reported several brain regions related to fatigue, such as thalamus, paracentral lobule and the medial global pallidus [96]. These areas are mainly linked to sensory and motor coordination. Same authors found the fornix and cingulum, both part of the limbic system, involved in the experience of this symptom [102]. Gulf War Illness is a chronic and multisymptomatic illness that affects military veterans of the Gulf War. This disorder is characterized by a wide range of symptoms, including significant fatigue, muscle pain and cognitive issues among others [124]. The experience of permanent fatigue is frequently described by Gulf War veterans [125–128]. Kelsall et al. reported that up to 66% of Gulf War patients suffer from mild to severe fatigue [125]. Furthermore, between 1.6 and 5.1% of these patients met the chronic fatigue syndrome criteria [126,129,130]. This review found only one study related to fatigue in Gulf War Illness [103]. The study found a correlation between fatigue and axial diffusivity in the inferior fronto-occipital fasciculus. This brain structure is related to the integration of auditory and visual association. Hepatitis C is caused by the hepatitis virus which, in turn, leads to the swollenness of the liver. a study found fatigue to be present in two thirds of patients with chronic Hepatitis C [131]. Another study reported that 53% of Hepatitis C patients suffer from fatigue. In 17% of these patients, fatigue was so severe that it led to activity impairment [132]. The only study reported in this review about Hepatitis C found the development of fatigue related to the ventral striatum [104], which mainly intercedes in reward cognition, reinforcement and motivation. HIV is a virus which attacks the immune system, which is the body's natural defence against infections and diseases. Prevalence of fatigue in HIV has varying rates according to the stage of the disease, ranging from no fatigue in the early stage of the disease, to almost 80% in AIDS patients [8,133–138]. Just one study regarding HIV met the inclusion criteria of this review and hence, was assessed [105]. Here, basal ganglia was associated with fatigue. Patients who suffered from paralytic poliomyelitis can develop postpoliomyelitis syndrome (PPS) years or even decades later. PPS is a disorder where patients suffer from a generalized fatigue, generally reported as the most burdensome symptom of the disease [139]. Approximately 66% to 89% of PPS patients suffer from high levels of fatigue [140–142]. Two studies regarding PPS-related fatigue were assessed. However, just one of them found significant findings. Reticular formation, putamen and medial leminiscus were indicated as possible correlates of fatigue. These structures are thought to be involved in several functions, such as behavioural arousal and consciousness, regulation of movements and somatosensation from the skin and joints. Chronic fatigue syndrome is a complex disorder whose most common symptom is extreme fatigue. In the UK, the prevalence of CFS has been rated between 11% [143] and 15% [144] per 100,000 people. This disorder has been widely studied and it has been the most reported illness in this article. a total of 13 CFS studies related to fatigue were gathered. The majority of them found areas related to executive and cognitive functions, memory and perception.

The brain structures found to be related to fatigue in the studies compared were highly heterogeneous, not only between diseases, but also for different studies within the same diseases. The most common structures were the frontal lobe, parietal lobe, limbic system and basal ganglia. These structures are associated with attention, memory, planning, integration of sensory information and learning.

Longitudinal studies, as opposed to cross-sectional studies, allow tracking of the same subjects over time, removing confounders such as cultural differences, age, etc. Therefore, they offer more precise and reliable indicators. In addition, they can give information about accumulative processes. What is more, they may allow the prediction of future changes in fatigue by assessing baseline factors. In spite of this, just seven out of 26 studies were longitudinal [91,93,99,100,104,105,114], and six

involved an interventional procedure. Within these six interventional studies, one was low quality and only employed MRS [105], one only recorded structural images and did not include a proper control group [104], and another only recorded structural images [93]. The fact that longitudinal designs allow follow-up of the patient during an intervention procedure, offering more precise indicators of the population changes, and their potential as prediction models, make them the best strategy to follow in the search of neural correlates of fatigue. Therefore, longitudinal neuroimaging studies following a fatigue treatment would be of inestimable worth in the study of this symptom.

sMRI, fMRI, DTI and FC studies identified significant neural correlates of fatigue, demonstrating that they are very useful techniques in the search for the processes responsible for fatigue within chronic illnesses. The integration of these techniques may be helpful in the search of biomarkers, rather than using them individually [145]. However, none of the studies in this review integrated all of them. sMRI, fMRI and DTI were integrated in [98] and sMRI, fMRI and FC in [106], both of them with no follow-up. Other studies have combined two of the techniques; sMRI and fMRI [96,108,111–113], sMRI and DTI [97,102,107], or sMRI and FC [40,72]. Integration of modalities is an attractive strategy to follow in the development of a comprehensive map of the pathophysiological brain networks of fatigue. This multimodal approach has demonstrated a more comprehensive understanding of brain changes in disorders such as amyotrophic lateral sclerosis [146], schizophrenia [147–157], bipolar disorder [158–161], characterization of tumours [162], traumatic brain injury [163], Parkinson's disease [164], psychosis [165,166], Alzheimer's disease [167,168] and mild cognitive impairment [169–171]. Therefore, it should be expected that the integration of techniques may help to elucidate further brain mechanisms of fatigue.

4.2. Limitations

This systematic review aimed to perform a comprehensive search of all studies employing MR techniques in the investigation of neural indicators of fatigue. Although a great number of references were gathered, it is still conceivable that other related papers have been overlooked. Furthermore, the inclusion criteria set a lower limit of studies with more than 10 subjects. This limit was based on fMRI which tend to have lower sample sizes than sMRI studies. This may mean that lower power, and therefore lower quality, sMRI studies may have been included than would otherwise be the case with a larger sample size threshold. We acknowledge the diversity in the way that fatigue was measured in the studies examined. Furthermore, studies employing fMRI make use of different tasks to induce fatigue. These facts increase the risk of bias and will inevitably contribute to a disparity in results. Finally, we acknowledge that the study of brain correlates by means of neuroimaging is insufficient to offer a comprehensive explanation of the mechanisms underlying fatigue. The integration of other types of biomarkers, such as biochemical ones, may provide further understanding of the phenomenon.

5. Conclusions

We have found that studies searching for neural indicators of fatigue within chronic diseases are of variable design and quality. Regarding the fatigue indicators, we found that there are not well-defined neural correlates of fatigue in any chronic diseases so far. Different designs and methodologies for the same illness offered different results. From this, we conclude that there are no common correlates of fatigue across chronic diseases. According to the employed design, it seems that the best strategy in the search of neural correlates of fatigue would be to integrate different neuroimaging techniques in a longitudinal study, with a fatigue alleviating intervention. Such an approach could be a great asset to unravel the neural mechanisms of this burdensome and neglected symptom.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ALS	Amyotrophic Lateral Sclerosis
AS	Ankylosing Spondylitis
BOLD	Blood Oxygen Level Dependent
CFS	Chronic Fatigue Syndrome
CNS	Central Nervous System
CT	Computed Tomography
DTI	Diffusion Tensor Imaging
FC	Functional Connectivity
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
GM	Grey Matter
GPA	Granulomatosis with Polyangiitis
HIV	Human Immunodeficiency Virus
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
PASAT	Paced Auditory Serial Attention Test
PET	Positron Emission Tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
qMT	Quantitative Magnetization Transfer
RA	Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus
sMRI	Structural Magnetic Resonance Imaging
SR	Systematic Review
VBM	Voxel Based Morphometry
WM	White Matter

References

1. Krupp, L.B.; Alvarez, L.A.; LaRocca, N.G.; Scheinberg, L.C. Fatigue in Multiple Sclerosis. *Arch. Neurol.* **1988**, *45*, 435–437. [CrossRef] [PubMed]
2. Berrios, G.E. Feelings of Fatigue and Psychopathology: a Conceptual History. *Compr. Psychiatry* **1990**, *31*, 140–151. [CrossRef]
3. Norheim, K.B.; Jonsson, G.; Omdal, R. Biological Mechanisms of Chronic Fatigue. *Rheumatology* **2011**, *50*, 1009–1018. [CrossRef] [PubMed]
4. Wolfe, F.; Hawley, D.J.; Wilson, K. The Prevalence and Meaning of Fatigue in Rheumatic Disease. *J. Rheumatol.* **1996**, *23*, 1407–1417. [PubMed]
5. Huyser, B.A.; Parker, J.C.; Thoreson, R.; Smarr, K.L.; Johnson, J.C.; Hoffman, R. Predictors of Subjective Fatigue among Individuals with Rheumatoid Arthritis. *Arthritis Rheumatol.* **1998**, *41*, 2230–2237. [CrossRef]
6. Krupp, L.B.; LaRocca, N.G.; Muir, J.; Steinberg, A.D. a Study of Fatigue in Systemic Lupus Erythematosus. *J. Rheumatol.* **1990**, *17*, 1450–1452. [PubMed]
7. Cauch-Dudek, K.; Abbey, S.; Stewart, D.E.; Heathcote, E.J. Fatigue in Primary Biliary Cirrhosis. *Gut* **1998**, *43*, 705–710. [CrossRef] [PubMed]
8. Breitbart, W.; McDonald, M.V.; Rosenfeld, B.; Monkman, N.D.; Passik, S. Fatigue in Ambulatory AIDS Patients. *J. Pain Symptom Manag.* **1998**, *15*, 159–167. [CrossRef]
9. Staud, R. Peripheral and Central Mechanisms of Fatigue in Inflammatory and Noninflammatory Rheumatic Diseases. *Curr. Rheumatol. Rep.* **2012**, *14*, 539–548. [CrossRef] [PubMed]
10. Matcham, F.; Ali, S.; Hotopf, M.; Chalder, T. Psychological Correlates of Fatigue in Rheumatoid Arthritis: a Systematic Review. *Clin. Psychol. Rev.* **2015**, *39*, 16–29. [CrossRef] [PubMed]

11. Nikolaus, S.; Bode, C.; Taal, E.; van de Laar, M.A.F.J. Fatigue and Factors Related to Fatigue in Rheumatoid Arthritis: a Systematic Review. *Arthritis Care Res.* **2013**, *65*, 1128–1146. [CrossRef] [PubMed]

12. Repping-Wuts, H.; Fransen, J.; Van Achterberg, T.; Bleijenberg, G.; Van Riel, P. Persistent Severe Fatigue in Patients with Rheumatoid Arthritis. *J. Clin. Nurs.* **2007**, *16*, 377–383. [CrossRef] [PubMed]

13. Pollard, L.C.; Choy, E.H.; Gonzalez, J.; Khoshaba, B.; Scott, D.L. Fatigue in Rheumatoid Arthritis Reflects Pain, Not Disease Activity. *Rheumatology* **2006**, *45*, 885–889. [CrossRef] [PubMed]

14. Bruce, N.; Mak, V.C.; Hallett, D.C.; Gladman, D.D.; Urowitz, M.B. Factors Associated with Fatigue in Patients with Systemic Lupus Erythematosus. *Ann. Rheum. Dis.* **1999**, *58*, 379–381. [CrossRef] [PubMed]

15. Wang, B.; Gladman, D.D.; Urowitz, M. Fatigue in Lupus Is Not Correlated with Disease Activity. *J. Rheumatol.* **1998**, *25*, 892–895. [PubMed]

16. Thyberg, I.; Dahlström, Ö.; Thyberg, M. Factors Related to Fatigue in Women and Men with Early Rheumatoid Arthritis: The Swedish Tira Study. *J. Rehabil. Med.* **2009**, *41*, 904–912. [CrossRef] [PubMed]

17. Van Hoogmoed, D.; Fransen, J.; Bleijenberg, G.; van Riel, P. Physical and Psychosocial Correlates of Severe Fatigue in Rheumatoid Arthritis. *Rheumatology* **2010**, *49*, 1294–1302. [CrossRef] [PubMed]

18. Belza, B.L.; Henke, C.J.; Yelin, E.H.; Epstein, W.V.; Gilliss, C.L. Correlates of Fatigue in Older Adults with Rheumatoid Arthritis. *Nurs. Res.* **1993**, *42*, 93–99. [CrossRef] [PubMed]

19. Zonana-Nacach, A.; Roseman, J.M.; McGwin, G.; Friedman, A.W.; Baethge, B.A.; Reveille, J.D.; Alarcón, G.S. Systemic Lupus Erythematosus in Three Ethnic Groups. VI: Factors Associated with Fatigue within 5 Years of Criteria Diagnosis. *Lupus* **2000**, *9*, 101–109. [CrossRef] [PubMed]

20. Bonafede, R.P.; Downey, D.C.; Bennett, R.M. An Association of Fibromyalgia with Primary Sjogren's Syndrome: a Prospective Study of 72 Patients. *J. Rheumatol.* **1995**, *22*, 133–136. [PubMed]

21. Jones, S.D.; Koh, W.H.; Steiner, A.; Garrett, S.L.; Calin, A. Fatigue in Ankylosing Spondylitis: Its Prevalence and Relationship to Disease Activity, Sleep, and Other Factors. *J. Rheumatol.* **1996**, *23*, 487–490. [PubMed]

22. Escobar, M.E.; Gerhardt, C.; Roesler, E.; Kuroda, M.P.; Silva, M.B.; Skare, T.L. Anemia versus Disease Activity as Cause of Fatigue in Rheumatoid Arthritis. *Acta Reumatol. Port.* **2010**, *35*, 24–28. [PubMed]

23. Mancuso, C.A.; Rincon, M.; Sayles, W.; Paget, S.A. Psychosocial Variables and Fatigue: a Longitudinal Study Comparing Individuals with Rheumatoid Arthritis and Healthy Controls. *J. Rheumatol.* **2006**, *33*, 1496–1502. [PubMed]

24. Stebbings, S.; Herbison, P.; Doyle, T.C.H.; Treharne, G.J.; Highton, J. a Comparison of Fatigue Correlates in Rheumatoid Arthritis and Osteoarthritis: Disparity in Associations with Disability, Anxiety and Sleep Disturbance. *Rheumatology* **2010**, *49*, 361–367. [CrossRef] [PubMed]

25. Brekke, M.; Hjortdahl, P.; Kvien, T.K. Self-Efficacy and Health Status in Rheumatoid Arthritis: a Two-Year Longitudinal Observational Study. *Rheumatology* **2001**, *40*, 387–392. [CrossRef] [PubMed]

26. Covic, T.; Tyson, G.; Spencer, D.; Howe, G. Depression in Rheumatoid Arthritis Patients: Demographic, Clinical, and Psychological Predictors. *J. Psychosom. Res.* **2006**, *60*, 469–476. [CrossRef] [PubMed]

27. Mckinley, P.S.; Ouellette, S.C.; Winkel, G.H. The Contributions of Disease Activity, Sleep Patterns, and Depression to Fatigue in Systemic Lupus Erythematosus. *Arthritis Rheum.* **1995**, *38*, 826–834. [CrossRef] [PubMed]

28. Barendregt, P.J.; Visser, M.R.; Smets, E.M.; Tulen, J.H.; van den Meiracker, A.H.; Boomsma, F.; Markusse, H.M. Fatigue in Primary Sjögren's Syndrome. *Ann. Rheum. Dis.* **1998**, *57*, 291–295. [CrossRef] [PubMed]

29. Neuberger, G.B. Measures of Fatigue: The Fatigue Questionnaire, Fatigue Severity Scale, Multidimensional Assessment of Fatigue Scale, and Short Form-36 Vitality (Energy/Fatigue) Subscale of the Short Form Health Survey. *Arthritis Care Res.* **2003**, *49*, S175–S183. [CrossRef]

30. Hewlett, S.; Dures, E.; Almeida, C. Measures of Fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for Severity, Effect, and Coping, Chalder Fatigue Questionnaire (CFQ), Checklist. *Arthritis Care Res.* **2011**, *63* (Suppl. 11), S263–S286. [CrossRef] [PubMed]

31. Kluger, B.M.; Krupp, L.B.; Enoka, R.M. Fatigue and Fatigability in Neurologic Illnesses: Proposal for a Unified Taxonomy. *Neurology* **2013**, *80*, 409–416. [CrossRef] [PubMed]

32. Schwid, S.R.; Tyler, C.M.; Scheid, E.A.; Weinstein, A.; Goodman, A.D.; McDermott, M.P. Cognitive Fatigue during a Test Requiring Sustained Attention: a Pilot Study. *Mult. Scler.* **2003**, *9*, 503–508. [CrossRef] [PubMed]

33. Bryant, D.; Chiaravalloti, N.D.; DeLuca, J. Objective Measurement of Cognitive Fatigue in Multiple Sclerosis. *Rehabil. Psychol.* **2004**, *49*, 114–122. [CrossRef]

34. Pardini, M.; Bonzano, L.; Mancardi, G.L.; Roccatagliata, L. Frontal Networks Play a Role in Fatigue Perception in Multiple Sclerosis. *Behav. Neurosci.* **2010**, *124*, 329–336. [CrossRef] [PubMed]

35. Lutz, J.; Jäger, L.; de Quervain, D.; Krauseneck, T.; Padberg, F.; Wichnalek, M.; Beyer, A.; Stahl, R.; Zirngibl, B.; Morhard, D.; et al. White and Gray Matter Abnormalities in the Brain of Patients with Fibromyalgia: a Diffusion-Tensor and Volumetric Imaging Study. *Arthritis Rheumatol.* **2008**, *58*, 3960–3969. [CrossRef] [PubMed]

36. Cook, D.B.; O'Connor, P.J.; Lange, G.; Steffener, J. Functional Neuroimaging Correlates of Mental Fatigue Induced by Cognition among Chronic Fatigue Syndrome Patients and Controls. *NeuroImage* **2007**, *36*, 108–122. [CrossRef] [PubMed]

37. Tartaglia, M.C.; Narayanan, S.; Arnold, D.L. Mental Fatigue Alters the Pattern and Increases the Volume of Cerebral Activation Required for a Motor Task in Multiple Sclerosis Patients with Fatigue. *Eur. J. Neurol.* **2008**, *15*, 413–419. [CrossRef] [PubMed]

38. Lange, G.; Wang, S.; DeLuca, J.; Natelson, B.H. Neuroimaging in Chronic Fatigue Syndrome. *Am. J. Med.* **1998**, *105*, 50S–53S. [CrossRef]

39. Boissoneault, J.; Letzen, J.; Lai, S.; O'Shea, A.; Craggs, J.; Robinson, M.E.; Staud, R. Abnormal Resting State Functional Connectivity in Patients with Chronic Fatigue Syndrome: An Arterial Spin-Labeling fMRI Study. *Magn. Reson. Imaging* **2016**, *34*, 603–608. [CrossRef] [PubMed]

40. Gay, C.W.; Robinson, M.E.; Lai, S.; O'Shea, A.; Craggs, J.G.; Price, D.D.; Staud, R. Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses. *Brain Connect.* **2016**, *6*, 48–56. [CrossRef] [PubMed]

41. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, Pl.J.; Kleijnen, J.; Moher, D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med.* **2009**, *6*, e1000100. [CrossRef] [PubMed]

42. Deck, M.D.; Henschke, C.; Lee, B.C.; Zimmerman, R.D.; Hyman, R.A.; Edwards, J.; Saint Louis, L.A.; Cahill, P.T.; Stein, H.; Whalen, J.P. Computed Tomography versus Magnetic Resonance Imaging of the Brain. a Collaborative Interinstitutional Study. *Clin. Imaging* **1989**, *13*, 2–15. [CrossRef]

43. Desmond, J.E.; Glover, G.H. Estimating Sample Size in Functional MRI (fMRI) Neuroimaging Studies: Statistical Power Analyses. *J. Neurosci. Methods* **2002**, *118*, 115–128. [CrossRef]

44. Hayasaka, S.; Peiffer, A.M.; Hugenschmidt, C.E.; Laurienti, P.J. Power and Sample Size Calculation for Neuroimaging Studies by Non-Central Random Field Theory. *NeuroImage* **2007**, *37*, 721–730. [CrossRef] [PubMed]

45. Jutzeler, C.R.; Curt, A.; Kramer, J.L.K. Relationship between Chronic Pain and Brain Reorganization after Deafferentation: a Systematic Review of Functional MRI Findings. *NeuroImage Clin.* **2015**, *9*, 599–606. [CrossRef] [PubMed]

46. Basu, N.; Alsyedalhashem, M.; D'allesandro, M.; Murray, A.D.; Clauw, D.J.; Waiter, G.D. Brain White Matter Integrity: a Future Biomarker for Rheumatoid Arthritis Related Fatigue? *Arthritis Rheumatol.* **2015**, *67*, 3902–3903.

47. Lange, G. FMRI Assessment of Cerebral Activation in Response to an Auditory Working Memory Task in Patients with Chronic Fatigue Syndrome. *NeuroImage* **1998**, *7*.

48. Rocca, M.A.; Fazio, R.; Alfieri, C.; Previtali, S.; Agosta, F.; Valsasina, P.; Falini, A.; Comi, G.; Filippi, M. Functional MRI Correlates of Fatigue in Patients with Hereditary and Acquired Peripheral Neuropathy. *Neurology* **2009**, *72*, A56.

49. Mathew, S.J.; Mao, X.; Keegan, K.A.; Levine, S.M.; Smith, E.L.P.; Heier, L.A.; Otcheretko, V.; Coplan, J.D.; Shungu, D.C. Ventricular Cerebrospinal Fluid Lactate Is Increased in Chronic Fatigue Syndrome Compared with Generalized Anxiety Disorder: An in Vivo 3.0 T 1H MRS Imaging Study. *NMR Biomed.* **2009**, *22*, 251–258. [CrossRef] [PubMed]

50. Mizuno, K.; Tanabe, H.C.; Tanaka, M.; Shigihara, Y.; Kawatani, J.; Jodoi, T.; Tomoda, A.; Miike, T.; Imai-Matsumura, K.; Sadato, N.; et al. Neural Substrates Associated with Divided Attention in Childhood Chronic Fatigue Syndrome. *Neurosci. Res.* **2009**, *65*, S239. [CrossRef]

51. Segal, B.M.; Mueller, B.A.; Pogatchnik, B.; Holker, E.; Zhu, X.; Prosser, R.; Veeramachaneni, R. Novel Brain Biomarkers for Fatigue and Cognitive Function In Primary Sjogren's Syndrome. In Proceedings of the Philadelphia ACR/ARHP Annual Science Meeting, Philadelphia, PA, USA, 16–21 October 2009.

52. Barnden, L.; Crouch, B.; Burnet, R.; Kwiatek, R.; Mernone, A.; Scroop, G.; Del Fante, P. The Enigma of Fatigue: Novel Analysis of Structural Mri Detects Extensive Changes in Chronic Fatigue Syndrome. *Intern. Med. J.* **2010**, *40*, 17.

53. Murrough, J.W.; Mao, X.; Collins, K.A.; Kelly, C.; Andrade, G.; Nestadt, P.; Levine, S.M.; Mathew, S.J.; Shungu, D.C. Increased Ventricular Lactate in Chronic Fatigue Syndrome Measured by 1H MRS Imaging at 3.0 T. II: Comparison with Major Depressive Disorder. *NMR Biomed.* **2010**, *23*, 643–650. [CrossRef] [PubMed]

54. Watanabe, Y. Brain Science of Fatigue and Chronic Fatigue by Molecular Imaging and Functional Neuroimaging. *Neurosci. Res.* **2010**, *68*, e52. [CrossRef]

55. Basu, N.; Jones, G.T.; Luqmani, R.A.; Murray, A.D.; Reid, D.M.; Macfarlane, G.J.; Waiter, G.D. Neural Correlates of Chronic Fatigue in Granulomatosis with Polyangiitis (GPA; Wegener's)—A Functional Magnetic Resonance Imaging (fMRI) Study. *Arthritis Rheum.* **2011**, *63*, 2370.

56. Cimprich, B.; Hayes, D.F.; Askren, M.K.; Jung, M.; Berman, M.G.; Therrien, B.; Reuter-Lorenz, P.A.; Zhang, M.; Peltier, S.; Noll, D. Altered Neurocognitive Responses Prior to Adjuvant Therapy for Breast Cancer: a Functional MRI Analysis of the Impact of Worry and Fatigue. *Cancer Res.* **2011**, *71*. [CrossRef]

57. Mizuno, K.; Tanaka, M.; Tanabe, H.C.; Kawatani, J.; Jodoi, T.; Tomoda, A.; Miike, T.; Matsumura, K.; Sadato, N.; Watanabe, Y. Divided Attention and Childhood Chronic Fatigue Syndrome (CCFS). *Neurosci. Res.* **2011**, *71*, e387. [CrossRef]

58. Prinsen, H.; Heerschap, A.; Bleijenberg, G.; Zwarts, M.; van der Graaf, M.; Rijpkema, M.; Van Laarhoven, H. Structural and Functional MRI of the Brain as Biomarker for Postcancer Fatigue. *J. Clin. Oncol.* **2011**, *29*, 9050. [CrossRef]

59. Basu, N.; Jones, G.; Luqmani, R.; Murray, A.; Reid, D.; Macfarlane, G.; Waiter, G. The Relationship between Brain White Matter Changes and Fatigue in Granulomatosis with Polyangiitis (GPA; Wegener's). *Ann. Rheum. Dis.* **2013**, *71*, 385–386. [CrossRef]

60. Nichols, E.H. Neurocognitive Impact in Adjuvant Chemotherapy for Breast Cancer Linked to Fatigue: a Prospective Functional MRI Study. *MD Conf. Express* **2013**, *12*, 11. [CrossRef]

61. Hampson, J.P.; Clauw, D.J.; Kim, J.; Napadow, V.; Harris, R.E. Frontal Brain Connectivity to the Default Mode Network Is Associated with Subjective Fatigue Irrespective of Pain and Depression. *Arthritis Rheum.* **2012**, *64*, S349–S350.

62. Unger, E.R.; Miller, A.H.; Jones, J.F.; Drake, D.F.; Tian, H.; Pagnoni, G. Decreased Basal Ganglia Activation in Chronic Fatigue Syndrome Subjects Is Associated with Increased Fatigue. *FASEB J.* **2012**, *26*, 1035–1120.

63. Haroon, E.; Wilson, A.E.; Udelson, H.; Chen, X.; Woolwine, B.; Parekh, S.; Hu, X.; Spivey, J.R.; Miller, A.H. Inflammation Induced Changes in Anterior Cingulate Cortex Glutamate Is Associated with Depression and Fatigue. *Brain. Behav. Immun.* **2013**, *32*, e33. [CrossRef]

64. Wu, Q.; Inman, R.D.; Davis, K.D. Grey Matter Correlates of Fatigue in Ankylosing Spondylitis Patients. In Proceedings of the Canada Annual Conference Canada Pain Society, Winnipeg, MB, Canada, 8–10 May 2013; p. 32.

65. Craggs, J.; Gay, C.; O'shea, A.; Madhavan, R.; Price, D.; Robinson, M.; Staud, R. Resting State Functional Connectivity Differs between Chronic Fatigue Syndrome Patients and Healthy Controls. *Arthritis Rheumatol.* **2014**, *66*, S397.

66. Craggs, J.; Lai, S.; Madhavan, R.; Price, D.; Robinson, M.; Staud, R. Cognitive Task Related Hypoperfusion of Frontal Gyrus in Patients with Chronic Fatigue. *Arthritis Rheumatol.* **2014**, *66*, S103.

67. Kocer, B.; Tezcan, M.E.; Caglayan, H.B.; Haznedaroglu, S.; Mercan, R.; Irkec, C. Cognitive Dysfunction and the Relationship of Fatigue and Depression in Primary Sjögren Syndrome. *Eur. J. Neurol.* **2014**, *21*, 464.

68. Meng, F.X.; Lu, Z.M.; Zhou, M.M.; Peng, M.; Yu, B.; Guo, Q.Y. Aberrant Whole-Brain Functional Connectivity in Children with Chronic Fatigue Syndrome. In Proceedings of the Abstract Archives of the RSNA, Radiological Society of North America 2013 Scientific Assembly and Annual Meeting, Chicago, IL, USA, 1–6 December 2013.

69. Mosher, V.; Swain, M.G.; Myers, R.P.; Macqueen, G.M.; Goodyear, B.G. Altered Functional Connections in the Brain of Patients with Primary Biliary Cirrhosis Are Associated with Fatigue. *Hepatology* **2014**, *60*, 339A–340A.

70. O'shea, A.; Craggs, J.; Madhavan, R.; Price, D.; Lai, S.; Robinson, M.; Staud, R. Chronic Fatigue Is Associated with Hypoperfusion of Parahippocampal Gyrus. *Arthritis Rheumatol.* **2014**, *66*, S105.

71. Gay, C.; O'Shea, A.; Robinson, M.; Craggs, J.; Staud, R. Default Mode Network Connectivity in Chronic Fatigue Syndrome Patients. *J. Pain* **2015**, *16*, S54. [CrossRef]

72. Staud, R.; Lai, S.; Price, D.; Robinson, M.; Craggs, J.; Boissoneault, J. Abnormal Resting State Functional Connectivity in Chronic Fatigue Syndrome Patients: An Arterial Spin-Labeling fMRI Study. *Arthritis Rheumatol.* **2015**, *67*, 1331.

73. Boissoneault, J.; Letzen, J.; O'Shea, A.; Lai, S.; Robinson, M.; Staud, R. Altered Resting State Functional Connectivity Is Correlated with Fatigue and Pain in Patients with Chronic Fatigue Syndrome. *J. Pain* **2016**, *17*, S38–S39. [CrossRef]

74. Sevel, L.; Letzen, J.; Boissoneault, J.; O'Shea, A.; Robinson, M.; Staud, R. (337) MRI Based Classification of Chronic Fatigue, Fibromyalgia Patients and Healthy Controls Using Machine Learning Algorithms: a Comparison Study. *J. Pain* **2016**, *17*, S60. [CrossRef]

75. Chaudhuri, A.; Condon, B.R.; Gow, J.W.; Brennan, D.; Hadley, D.M. Proton Magnetic Resonance Spectroscopy of Basal Ganglia in Chronic Fatigue Syndrome. *Neuroreport* **2003**, *14*, 225–228. [CrossRef] [PubMed]

76. Thomas, R.J. Fatigue in the Executive Cortical Network Demonstrated in Narcoleptics Using Functional Magnetic Resonance Imaging—A Preliminary Study. *Sleep Med.* **2005**, *6*, 399–406. [CrossRef] [PubMed]

77. Tanaka, M.; Sadato, N.; Okada, T.; Mizuno, K.; Sasabe, T.; Tanabe, H.C.; Saito, D.N.; Onoe, H.; Kuratsune, H.; Watanabe, Y. Reduced Responsiveness Is an Essential Feature of Chronic Fatigue Syndrome: a fMRI Study. *BMC Neurol.* **2006**, *6*, 9. [CrossRef] [PubMed]

78. Puri, B.K.; Agour, M.; Gunatilake, K.D.R.; Fernando, K.A.C.; Gurusinghe, A.I.; Treasaden, I.H. Reduction in Left Supplementary Motor Area Grey Matter in Adult Female Fibromyalgia Sufferers with Marked Fatigue and without Affective Disorder: a Pilot Controlled 3-T Magnetic Resonance Imaging Voxel-Based Morphometry Study. *J. Int. Med. Res.* **2010**, *38*, 1468–1472. [CrossRef] [PubMed]

79. Hampson, J.P.; Zick, S.M.; Khabir, T.; Wright, B.D.; Harris, R.E. Altered Resting Brain Connectivity in Persistent Cancer Related Fatigue. *NeuroImage Clin.* **2015**, *8*, 305–313. [CrossRef] [PubMed]

80. Greco, A.; Tannock, C.; Brostoff, J.; Costa, D.C. Brain MR in Chronic Fatigue Syndrome. *Am. J. Neuroradiol.* **1997**, *18*, 1265–1269. [PubMed]

81. Lange, G.; DeLuca, J.; Maldjian, J.A.; Lee, H.; Tiersky, L.A.; Natelson, B.H. Brain MRI Abnormalities Exist in a Subset of Patients with Chronic Fatigue Syndrome. *J. Neurol. Sci.* **1999**, *171*, 3–7. [CrossRef]

82. Perrin, R.; Embleton, K.; Pentreath, V.W.; Jackson, A. Longitudinal MRI Shows No Cerebral Abnormality in Chronic Fatigue Syndrome. *Br. J. Radiol.* **2010**, *83*, 419–423. [CrossRef] [PubMed]

83. Biswal, B.; Kunwar, P.; Natelson, B.H. Cerebral Blood Flow Is Reduced in Chronic Fatigue Syndrome as Assessed by Arterial Spin Labeling. *J. Neurol. Sci.* **2011**, *301*, 9–11. [CrossRef] [PubMed]

84. Puri, B.K.; Jakeman, P.M.; Agour, M.; Gunatilake, K.D.R.; Fernando, K.A.C.; Gurusinghe, A.I.; Treasaden, I.H.; Waldman, A.D.; Gishen, P. Regional Grey and White Matter Volumetric Changes in Myalgic Encephalomyelitis (Chronic Fatigue Syndrome): a Voxel-Based Morphometry 3 T MRI Study. *Br. J. Radiol.* **2012**, *85*, e270–e273. [CrossRef] [PubMed]

85. Shungu, D.C.; Weiduschat, N.; Murrough, J.W.; Mao, X.; Pillemer, S.; Dyke, J.P.; Medow, M.S.; Natelson, B.H.; Stewart, J.M.; Mathew, S.J. Increased Ventricular Lactate in Chronic Fatigue Syndrome. III. Relationships to Cortical Glutathione and Clinical Symptoms Implicate Oxidative Stress in Disorder Pathophysiology. *NMR Biomed.* **2012**, *10*, 1073–1087. [CrossRef] [PubMed]

86. van Der Schaaf, M.E.; Schmits, I.C.; Roerink, M.; Geurts, D.E.M.; Toni, I.; Roelofs, K.; De Lange, F.P.; Nater, U.M.; van der Meer, J.W.M.; Knoop, H. Investigating Neural Mechanisms of Change of Cognitive Behavioural Therapy for Chronic Fatigue Syndrome: a Randomized Controlled Trial. *BMC Psychiatry* **2015**, *15*, 144. [CrossRef] [PubMed]

87. Miike, T.; Tomoda, A.; Jhodoi, T.; Iwatani, N.; Mabe, H. Learning and Memorization Impairment in Childhood Chronic Fatigue Syndrome Manifesting as School Phobia in Japan. *Brain Dev.* **2004**, *10*, 442–447. [CrossRef] [PubMed]

88. Weissenborn, K.; Ennen, J.C.; Bokemeyer, M.; Ahl, B.; Wurster, U.; Tillmann, H.; Trebst, C.; Hecker, H.; Berding, G. Monoaminergic Neurotransmission Is Altered in Hepatitis C Virus Infected Patients with Chronic Fatigue and Cognitive Impairment. *Gut* **2006**, *55*, 1624–1630. [CrossRef] [PubMed]

89. Omdal, R.; Mellgren, S.I.; Koldingsnes, W.; Jacobsen, E.A.; Husby, G. Fatigue in Patients with Systemic Lupus Erythematosus: Lack of Associations to Serum Cytokines, Antiphospholipid Antibodies, or Other Disease Characteristics. *J. Rheumatol.* **2002**, *29*, 482–486. [PubMed]

90. De Lange, F.P.; Kalkman, J.S.; Bleijenberg, G.; Hagoort, P.; Van der Meer, J.W.M.; Toni, I. Gray Matter Volume Reduction in the Chronic Fatigue Syndrome. *NeuroImage* **2005**, *26*, 777–781. [CrossRef] [PubMed]

91. De Lange, F.P.; Koers, A.; Kalkman, J.S.; Bleijenberg, G.; Hagoort, P.; Van der Meer, J.W.M.; Toni, I. Increase in Prefrontal Cortical Volume Following Cognitive Behavioural Therapy in Patients with Chronic Fatigue Syndrome. *Brain* **2008**, *131*, 2172–2180. [CrossRef] [PubMed]

92. Bruno, R.L.; Cohen, J.M.; Galski, T.; Frick, N.M. The Neuroanatomy of Post-Polio Fatigue. *Arch. Phys. Med. Rehabil.* **1994**, *75*, 498–504. [PubMed]

93. Wu, Q.; Inman, R.D.; Davis, K.D. Tumor Necrosis Factor Inhibitor Therapy in Ankylosing Spondylitis: Differential Effects on Pain and Fatigue and Brain Correlates. *Pain* **2015**, *156*, 297–304. [CrossRef] [PubMed]

94. Okada, T.; Tanaka, M.; Kuratsune, H.; Watanabe, Y.; Sadato, N. Mechanisms Underlying Fatigue: a Voxel-Based Morphometric Study of Chronic Fatigue Syndrome. *BMC Neurol.* **2004**, *4*, 14. [CrossRef] [PubMed]

95. Trojan, D.A.; Narayanan, S.; Francis, S.J.; Caramanos, Z.; Robinson, A.; Cardoso, M.; Arnold, D.L. Brain Volume and Fatigue in Patients with Postpoliomyelitis Syndrome. *PM&R* **2014**, *6*, 215–220.

96. Basu, N.; Murray, A.D.; Jones, G.T.; Reid, D.M.; Macfarlane, G.J.; Waiter, G.D. Neural Correlates of Fatigue in Granulomatosis with Polyangiitis: a Functional Magnetic Resonance Imaging Study. *Rheumatology* **2014**, *53*, 2080–2087. [CrossRef] [PubMed]

97. Wu, Q.; Inman, R.D.; Davis, K.D. Fatigue in Ankylosing Spondylitis Is Associated with the Brain Networks of Sensory Salience and Attention. *Arthritis Rheumatol.* **2014**, *66*, 295–303. [CrossRef] [PubMed]

98. Menning, S.; de Ruiter, M.B.; Veltman, D.J.; Koppelmans, V.; Kirschbaum, C.; Boogerd, W.; Reneman, L.; Schagen, S.B. Multimodal MRI and Cognitive Function in Patients with Breast Cancer prior to Adjuvant Treatment—The Role of Fatigue. *NeuroImage Clin.* **2015**, *7*, 547–554. [CrossRef] [PubMed]

99. Askren, M.K.; Jung, M.; Berman, M.G.; Zhang, M.; Therrien, B.; Peltier, S.; Ossher, L.; Hayes, D.F.; Reuter-Lorenz, P.A.; Cimprich, B. Neuromarkers of Fatigue and Cognitive Complaints Following Chemotherapy for Breast Cancer: a Prospective fMRI Investigation. *Breast Cancer Res Treat* **2014**, *147*, 445–455. [CrossRef] [PubMed]

100. Prinsen, H.; Heerschap, A.; Bleijenberg, G.; Zwarts, M.J.; Leer, J.W.H.; van Asten, J.J.; van der Graaf, M.; Rijpkema, M.; van Laarhoven, H.W.M. Magnetic Resonance Spectroscopic Imaging and Volumetric Measurements of the Brain in Patients with Postcancer Fatigue: a Randomized Controlled Trial. *PLoS ONE* **2013**, *8*, e74638. [CrossRef] [PubMed]

101. Forton, D.M.; Patel, N.; Prince, M.; Oatridge, A.; Hamilton, G.; Goldblatt, J.; Allsop, J.; Hajnal, J.V.; Thomas, H.C.; Bassendine, M.; et al. Fatigue and Primary Biliary Cirrhosis: Association of Globus Pallidus Magnetisation Transfer Ratio Measurements with Fatigue Severity and Blood Manganese Levels. *Gut* **2004**, *53*, 587–592. [CrossRef] [PubMed]

102. Basu, N.; Murray, A.D.; Jones, G.T.; Reid, D.M.; Macfarlane, G.J.; Waiter, G.D. Fatigue-Related Brain White Matter Changes in Granulomatosis with Polyangiitis. *Rheumatology* **2013**, *52*, 1429–1434. [CrossRef] [PubMed]

103. Rayhan, R.U.; Stevens, B.W.; Timbol, C.R.; Adewuyi, O.; Walitt, B.; VanMeter, J.W.; Baraniuk, J.N. Increased Brain White Matter Axial Diffusivity Associated with Fatigue, Pain and Hyperalgesia in Gulf War Illness. *PLoS ONE* **2013**, *8*, e58493. [CrossRef] [PubMed]

104. Dowell, N.G.; Cooper, E.A.; Tibble, J.; Voon, V.; Critchley, H.D.; Cercignani, M.; Harrison, N.A. Acute Changes in Striatal Microstructure Predict the Development of Interferon-Alpha Induced Fatigue. *Biol. Psychiatry* **2016**, *79*, 1320–1328. [CrossRef] [PubMed]

105. Schifitto, G.; Deng, L.; Yeh, T.; Evans, S.R.; Ernst, T.; Zhong, J.; Clifford, D. Clinical, Laboratory, and Neuroimaging Characteristics of Fatigue in HIV-Infected Individuals. *J. Neurovirol.* **2011**, *17*, 17–25. [CrossRef] [PubMed]

106. Kim, B.; Namkoong, K.; Kim, J.; Lee, S.; Yoon, K.J.; Choi, M.; Jung, Y. Altered Resting-State Functional Connectivity in Women with Chronic Fatigue Syndrome. *Psychiatry Res. Neuroimaging* **2015**, *234*, 292–297. [CrossRef] [PubMed]

107. Zeineh, M.M.; Kang, J.; Atlas, S.W.; Raman, M.M.; Reiss, A.L.; Norris, J.L.; Valencia, I.; Montoya, J.G. Right Arcuate Fasciculus Abnormality in Chronic Fatigue Syndrome. *Radiology* **2014**, *274*, 517–526. [CrossRef] [PubMed]

108. Miller, A.H.; Jones, J.F.; Drake, D.F.; Tian, H.; Unger, E.R.; Pagnoni, G. Decreased Basal Ganglia Activation in Subjects with Chronic Fatigue Syndrome: Association with Symptoms of Fatigue. *PLoS ONE* **2014**, *9*, e98156. [CrossRef] [PubMed]

109. Barnden, L.R.; Crouch, B.; Kwiatek, R.; Burnet, R.; Mernone, A.; Chryssidis, S.; Scroop, G.; Del Fante, P. a Brain MRI Study of Chronic Fatigue Syndrome: Evidence of Brainstem Dysfunction and Altered Homeostasis. *NMR Biomed.* **2011**, *24*, 1302–1312. [CrossRef] [PubMed]

110. Caseras, X.; Mataix-Cols, D.; Rimes, K.A.; Giampietro, V.; Brammer, M.; Zelaya, F.; Chalder, T.; Godfrey, E. The Neural Correlates of Fatigue: An Exploratory Imaginal Fatigue Provocation Study in Chronic Fatigue Syndrome. *Psychol. Med.* **2008**, *38*, 941–951. [CrossRef] [PubMed]

111. Caseras, X.; Mataix-Cols, D.; Giampietro, V.; Rimes, K.A.; Brammer, M.; Zelaya, F.; Chalder, T.; Godfrey, E.L. Probing the Working Memory System in Chronic Fatigue Syndrome: a Functional Magnetic Resonance Imaging Study Using the N-Back Task. *Psychosom. Med.* **2006**, *68*, 947–955. [CrossRef] [PubMed]

112. Lange, G.; Steffener, J.; Cook, D.B.; Bly, B.M.; Christodoulou, C.; Liu, W.C.; Deluca, J.; Natelson, B.H. Objective Evidence of Cognitive Complaints in Chronic Fatigue Syndrome: a BOLD fMRI Study of Verbal Working Memory. *NeuroImage* **2005**, *26*, 513–524. [CrossRef] [PubMed]

113. De Lange, F.P.; Kalkman, J.S.; Bleijenberg, G.; Hagoort, P.; Werf, S.P.; Van der Meer, J.W.M.; Toni, I. Neural Correlates of the Chronic Fatigue Syndrome—An fMRI Study. *Brain* **2004**, *127*, 1948–1957. [CrossRef] [PubMed]

114. Cope, H.; Pernet, A.; Kendall, B.; David, A. Cognitive Functioning and Magnetic Resonance Imaging in Chronic Fatigue. *Br. J. Psychiatry* **1995**, *167*, 86–94. [CrossRef] [PubMed]

115. Calin, A.; Edmunds, L.; Kennedy, L.G. Fatigue in Ankylosing Spondylitis—Why Is It Ignored? *J. Rheumatol.* **1993**, *20*, 991–995. [PubMed]

116. Dernis-Labous, E.; Messow, M.; Dougados, M. Assessment of Fatigue in the Management of Patients with Ankylosing Spondylitis. *Rheumatology* **2003**, *42*, 1523–1528. [CrossRef] [PubMed]

117. Wagner, L.; Cella, D. Fatigue and Cancer: Causes, Prevalence and Treatment Approaches. *Br. J. Cancer* **2004**, *91*, 822–828. [CrossRef] [PubMed]

118. Hofman, M.; Ryan, J.L.; Figueroa-Moseley, C.D.; Jean-Pierre, P.; Morrow, G.R. Cancer-Related Fatigue: The Scale of the Problem. *Oncologist* **2007**, *12* (Suppl. 1), 4–10. [CrossRef] [PubMed]

119. Blesch, K.S.; Paice, J.A.; Wickham, R.; Harte, N.; Schnoor, D.K.; Purl, S.; Rehwalt, M.; Kopp, P.L.; Manson, S.; Coveny, S.B. Correlates of Fatigue in People with Breast or Lung Cancer. *Oncol. Nurs. Forum* **1991**, *18*, 81–87. [PubMed]

120. Huet, P.M.; Deslauriers, J.; Tran, A.; Faucher, C.; Charbonneau, J. Impact of Fatigue on the Quality of Life of Patients with Primary Biliary Cirrhosis. *Am. J. Gastroenterol.* **2000**, *95*, 760–767. [CrossRef] [PubMed]

121. Segal, B.; Thomas, W.; Rogers, T.; Leon, J.M.; Hughes, P.; Patel, D.; Patel, K.; Novitzke, J.; Rohrer, M.; Gopalakrishnan, R.; et al. Prevalence, Severity, and Predictors of Fatigue in Subjects with Primary Sjögren's Syndrome. *Arthritis Care Res.* **2008**, *59*, 1780–1787. [CrossRef] [PubMed]

122. Tench, C.M.; McCurdie, I.; White, P.D.; D'Cruz, D.P. The Prevalence and Associations of Fatigue in Systemic Lupus Erythematosus. *Rheumatology* **2000**, *39*, 1249–1254. [CrossRef] [PubMed]

123. Herlyn, K.; Hellmich, B.; Seo, P.; Merkel, P.A. Patient-Reported Outcome Assessment in Vasculitis May Provide Important Data and a Unique Perspective. *Arthritis Care Res.* **2010**, *62*, 1639–1645. [CrossRef] [PubMed]

124. David, A.; Ferry, S.; Wessely, S. Gulf War Illness. *BMJ* **1997**, *314*, 239–240.

125. Kelsall, H.L.; Sim, M.R.; Forbes, A.B.; Glass, D.C.; McKenzie, D.P.; Ikin, J.F.; Abramson, M.J.; Blizzard, L.; Ittak, P. Symptoms and Medical Conditions in Australian Veterans of the 1991 Gulf War: Relation to Immunisations and Other Gulf War Exposures. *Occup. Environ. Med.* **2004**, *61*, 1006–1013. [CrossRef] [PubMed]

126. Fukuda, K.; Nisenbaum, R.; Stewart, G.; Thompson, W.W.; Robin, L.; Washko, R.M.; Noah, D.L.; Barrett, D.H.; Randall, B.; Herwaldt, B.L.; et al. Chronic Multisymptom Illness Affecting Air Force Veterans of the Gulf War. *J. Am. Med. Assoc.* **1998**, *280*, 981–988. [CrossRef]

127. Gray, G.C.; Reed, R.J.; Kaiser, K.S.; Smith, T.C.; Gastañaga, V.M. Self-Reported Symptoms and Medical Conditions among 11,868 Gulf War-Era Veterans: The Seabee Health Study. *Am. J. Epidemiol.* **2002**, *155*, 1033–1044. [CrossRef] [PubMed]

128. The Iowa Persian Gulf Study Group. Self-Reported Illness and Health Status among Gulf War Veterans. a Population-Based Study. The Iowa Persian Gulf Study Group. *JAMA* **1997**, *277*, 238–245.

129. Eisen, S.A.; Kang, H.K.; Murphy, F.M.; Blanchard, M.S.; Reda, D.J.; Henderson, W.G.; Toomey, R.; Jackson, L.W.; Alpern, R.; Parks, B.J.; et al. Gulf War Veterans' Health: Medical Evaluation of a U.S. Cohort. *Ann. Intern. Med.* **2005**, *142*, 881–890. [CrossRef] [PubMed]

130. McCauley, L.A.; Joos, S.K.; Barkhuizen, A.; Shuell, T.; Tyree, W.A.; Bourdette, D.N. Chronic Fatigue in a Population-Based Study of Gulf War Veterans. *Arch. Environ. Health* **2002**, *57*, 340–348. [CrossRef] [PubMed]

131. Barkhuizen, A.; Rosen, H.R.; Wolf, S.; Flora, K.; Benner, K.; Bennett, R.M. Musculoskeletal Pain and Fatigue Are Associated with Chronic Hepatitis C: a Report of 239 Hepatology Clinic Patients. *Am. J. Gastroenterol.* **1999**, *94*, 1355–1360. [CrossRef]

132. Poynard, T.; Cacoub, P.; Ratziu, V.; Myers, R.P.; Dezailles, M.H.; Mercadier, A.; Ghillani, P.; Charlotte, F.; Piette, J.C.; Moussalli, J. Fatigue in Patients with Chronic Hepatitis C. *J. Viral Hepat.* **2002**, *9*, 295–303. [CrossRef] [PubMed]

133. Darko, D.F.; McCutchan, J.A.; Kripke, D.F.; Gillin, J.C.; Golshan, S. Fatigue, Sleep Disturbance, Disability, and Indices of Progression of HIV Infection. *Am. J. Psychiatry* **1992**, *149*, 514–520. [PubMed]

134. Ferrando, S.; Evans, S.; Goggin, K.; Sewell, M.; Fishman, B.; Rabkin, J. Fatigue in HIV Illness: Relationship to Depression, Physical Limitations, and Disability. *Psychosom. Med.* **1998**, *60*, 759–764. [CrossRef] [PubMed]

135. Phillips, K.D.; Sowell, R.L.; Rojas, M.; Tavakoli, A.; Fulk, L.J.; Hand, G.A. Physiological and Psychological Correlates of Fatigue in HIV Disease. *Biol. Res. Nurs.* **2004**, *6*, 59–74. [CrossRef] [PubMed]

136. Justice, A.C.; Rabeneck, L.; Hays, R.D.; Wu, A.W.; Bozzette, S.A. Sensitivity, Specificity, Reliability, and Clinical Validity of Provider-Reported Symptoms: a Comparison with Self-Reported Symptoms. Outcomes Committee of the AIDS Clinical Trials Group. *J. Acquir. Immune Defic. Syndr.* **1999**, *21*, 126–133. [PubMed]

137. Voss, J.G. Predictors and Correlates of Fatigue in HIV/AIDS. *J. Pain Symptom Manag.* **2005**, *29*, 173–184. [CrossRef] [PubMed]

138. Sullivan, P.S.; Dworkin, M.S. Adult and Adolescent Spectrum of HIV Disease Investigators. Prevalence and Correlates of Fatigue among Persons with HIV Infection. *J. Pain Symptom Manag.* **2003**, *25*, 329–333. [CrossRef]

139. Berlly, M.H.; Strauser, W.W.; Hall, K.M. Fatigue in Postpolio Syndrome. *Arch. Phys. Med. Rehabil.* **1991**, *72*, 115–118. [PubMed]

140. Agre, J.C.; Rodriquez, A.A.; Sperling, K.B. Symptoms and Clinical Impressions of Patients Seen in a Postpolio Clinic. *Arch. Phys. Med. Rehabil.* **1989**, *70*, 367–370. [PubMed]

141. Ramlow, J.; Laporte, A.M.; Kaufmann, R.; Kuller, L. Epidemiology of the Post-Polio Syndrome. *Am. J. Epidemiol.* **1992**, *1136*, 769–786. [CrossRef]

142. Vasconcelos, O.M.; Prokhorenko, O.A.; Kelley, K.F.; Vo, A.H.; Olsen, C.H.; Dalakas, M.C.; Halstead, L.S.; Jabbari, B.; Campbell, W.W. a Comparison of Fatigue Scales in Postpoliomyelitis Syndrome. *Arch. Phys. Med. Rehabil.* **2006**, *87*, 1213–1217. [CrossRef] [PubMed]

143. Wessely, S.; Chalder, T.; Hirsch, S.; Wallace, P.; Wright, D. The Prevalence and Morbidity of Chronic Fatigue and Chronic Fatigue Syndrome: a Prospective Primary Care Study. *Am. J. Public Health* **1997**, *87*, 1449–1455. [CrossRef] [PubMed]

144. Watanabe, N.; Stewart, R.; Jenkins, R.; Bhugra, D.K.; Furukawa, T.A. The Epidemiology of Chronic Fatigue, Physical Illness, and Symptoms of Common Mental Disorders: a Cross-Sectional Survey from the Second British National Survey of Psychiatric Morbidity. *J. Psychosom. Res.* **2008**, *64*, 357–362. [CrossRef] [PubMed]

145. Damoiseaux, J.S.; Greicius, M.D. Greater than the Sum of Its Parts: a Review of Studies Combining Structural Connectivity and Resting-State Functional Connectivity. *Brain Struct. Funct.* **2009**, *213*, 525–533. [CrossRef] [PubMed]

146. Douaud, G.; Filippini, N.; Knight, S.; Talbot, K.; Turner, M.R. Integration of Structural and Functional Magnetic Resonance Imaging in Amyotrophic Lateral Sclerosis. *Brain* **2011**, *134*, 3470–3479. [CrossRef] [PubMed]

147. Tian, L.; Meng, C.; Yan, H.; Zhao, Q.; Liu, Q.; Yan, J.; Han, Y.; Yuan, H.; Wang, L.; Yue, W.; et al. Convergent Evidence from Multimodal Imaging Reveals Amygdala Abnormalities in Schizophrenic Patients and Their First-Degree Relatives. *PLoS ONE* **2011**, *6*, e28794. [CrossRef] [PubMed]

148. Salgado-Pineda, P.; Junque, C.; Vendrell, P.; Baeza, I.; Bargallo, N.; Falcon, C.; Bernardo, M. Decreased Cerebral Activation during CPT Performance: Structural and Functional Deficits in Schizophrenic Patients. *NeuroImage* **2004**, *21*, 840–847. [CrossRef] [PubMed]

149. Salgado-Pineda, P.; Fakra, E.; Delaveau, P.; McKenna, P.J.; Pomarol-Clotet, E.; Blin, O. Correlated Structural and Functional Brain Abnormalities in the Default Mode Network in Schizophrenia Patients. *Schizophr. Res.* **2011**, *125*, 101–109. [CrossRef] [PubMed]

150. Rasser, P.E.; Johnston, P.; Lagopoulos, J.; Ward, P.B.; Schall, U.; Thienel, R.; Bender, S.; Toga, A.W.; Thompson, P.M. Functional MRI BOLD Response to Tower of London Performance of First-Episode Schizophrenia Patients Using Cortical Pattern Matching. *NeuroImage* **2005**, *26*, 941–951. [CrossRef] [PubMed]

151. Michael, A.M.; Baum, S.A.; White, T.; Demirci, O.; Andreasen, N.C.; Segall, J.M.; Jung, R.E.; Pearlson, G.; Clark, V.P.; Gollub, R.L.; et al. Does Function Follow Form?: Methods to Fuse Structural and Functional Brain Images Show Decreased Linkage in Schizophrenia. *NeuroImage* **2010**, *49*, 2626–2637. [CrossRef] [PubMed]

152. Calhoun, V.D.; Adali, T.; Giuliani, N.R.; Pekar, J.J.; Kiehl, K.A.; Pearlson, G.D. Method for Multimodal Analysis of Independent Source Differences in Schizophrenia: Combining Gray Matter Structural and Auditory Oddball Functional Data. *Hum. Brain Mapp.* **2006**, *27*, 47–62. [CrossRef] [PubMed]

153. Correa, N.M.; Li, Y.O.; Adali, T.; Calhoun, V.D. Canonical Correlation Analysis for Feature-Based Fusion of Biomedical Imaging Modalities and Its Application to Detection of Associative Networks in Schizophrenia. *IEEE J. Sel. Top. Signal Process.* **2008**, *2*, 998–1007. [CrossRef] [PubMed]

154. Camchong, J.; MacDonald, A.W.; Bell, C.; Mueller, B.A.; Lim, K.O. Altered Functional and Anatomical Connectivity in Schizophrenia. *Schizophr. Bull.* **2011**, *37*, 640–650. [CrossRef] [PubMed]

155. Koch, K.; Wagner, G.; Schachtzabel, C.; Schultz, C.C.; Güllmar, D.; Reichenbach, J.R.; Sauer, H.; Schlösser, R.G.M. Neural Activation and Radial Diffusivity in Schizophrenia: Combined fMRI and Diffusion Tensor Imaging Study. *Br. J. Psychiatry* **2011**, *198*, 223–229. [CrossRef] [PubMed]

156. Schlösser, R.G.M.; Nenadic, I.; Wagner, G.; Güllmar, D.; von Consbruch, K.; Köhler, S.; Schultz, C.C.; Koch, K.; Fitzek, C.; Matthews, P.M.; et al. White Matter Abnormalities and Brain Activation in Schizophrenia: a Combined DTI and fMRI Study. *Schizophr. Res.* **2007**, *89*, 1–11. [CrossRef] [PubMed]

157. Yan, H.; Tian, L.; Yan, J.; Sun, W.; Liu, Q.; Zhang, Y.B.; Li, X.M.; Zang, Y.F.; Zhang, D. Functional and Anatomical Connectivity Abnormalities in Cognitive Division of Anterior Cingulate Cortex in Schizophrenia. *PLoS ONE* **2012**, *7*, e45659. [CrossRef] [PubMed]

158. Wang, F.; Kalmar, J.H.; He, Y.; Jackowski, M.; Chepenik, L.G.; Edmiston, E.E.; Tie, K.; Gong, G.; Shah, M.P.; Jones, M.; et al. Functional and Structural Connectivity between the Perigenual Anterior Cingulate and Amygdala in Bipolar Disorder. *Biol. Psychiatry* **2009**, *66*, 516–521. [CrossRef] [PubMed]

159. Sui, J.; Pearlson, G.; Caprihan, A.; Adali, T.; Kiehl, K.A.; Liu, J.; Yamamoto, J.; Calhoun, V.D. Discriminating Schizophrenia and Bipolar Disorder by Fusing fMRI and DTI in a Multimodal CCA+ Joint ICA Model. *NeuroImage* **2011**, *57*, 839–855. [CrossRef] [PubMed]

160. Chen, Z.; Cui, L.; Li, M.; Jiang, L.; Deng, W.; Ma, X.; Wang, Q.; Huang, C.; Wang, Y.; Collier, D.A.; et al. Voxel Based Morphometric and Diffusion Tensor Imaging Analysis in Male Bipolar Patients with First-Episode Mania. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2012**, *36*, 231–238. [CrossRef] [PubMed]

161. Haller, S.; Xekardaki, A.; Delaloye, C.; Canuto, A.; Lövblad, K.O.; Gold, G.; Giannakopoulos, P. Combined Analysis of Grey Matter Voxel-Based Morphometry and White Matter Tract-Based Spatial Statistics in Late-Life Bipolar Disorder. *J. Psychiatry Neurosci.* **2011**, *36*, 391–401. [CrossRef] [PubMed]

162. Schonberg, T.; Pianka, P.; Hendler, T.; Pasternak, O.; Assaf, Y. Characterization of Displaced White Matter by Brain Tumors Using Combined DTI and fMRI. *NeuroImage* **2006**, *30*, 1100–1111. [CrossRef] [PubMed]

163. Palacios, E.M.; Sala-Llonch, R.; Junque, C.; Roig, T.; Tormos, J.M.; Bargallo, N.; Vendrell, P. White Matter Integrity Related to Functional Working Memory Networks in Traumatic Brain Injury. *Neurology* **2012**, *78*, 852–860. [CrossRef] [PubMed]

164. Rektorova, I.; Mikl, M.; Barrett, J.; Marecek, R.; Rektor, I.; Paus, T. Functional Neuroanatomy of Vocalization in Patients with Parkinson's Disease. *J. Neurol. Sci.* **2012**, *313*, 7–12. [CrossRef] [PubMed]

165. Schultz, C.C.; Fusar-Poli, P.; Wagner, G.; Koch, K.; Schachtzabel, C.; Gruber, O.; Sauer, H.; Schlösser, R.G.M. Multimodal Functional and Structural Imaging Investigations in Psychosis Research. *Eur. Arch. Psychiatry Clin. Neurosci.* **2012**, *262*, S97–S106. [CrossRef] [PubMed]

166. Fusar-Poli, P.; Broome, M.R.; Woolley, J.B.; Johns, L.C.; Tabraham, P.; Bramon, E.; Valmaggia, L.; Williams, S.C.; McGuire, P. Altered Brain Function Directly Related to Structural Abnormalities in People at Ultra High Risk of Psychosis: Longitudinal VBM-fMRI Study. *J. Psychiatr. Res.* **2011**, *45*, 190–198. [CrossRef] [PubMed]

167. Soldner, J.; Meindl, T.; Koch, W.; Bokde, A.L.; Reiser, M.F.; Moller, H.J.; Burger, K.; Hampel, H.; Teipel, S. Structural and Functional Neuronal Connectivity in Alzheimer's Disease: a Combined DTI and fMRI Study. *Nervenarzt* **2012**, *83*, 878–887. [CrossRef] [PubMed]

168. Cui, Y.; Liu, B.; Luo, S.; Zhen, X.; Fan, M.; Liu, T.; Zhu, W.; Park, M.; Jiang, T.; Jin, J.S. Identification of Conversion from Mild Cognitive Impairment to Alzheimer's Disease Using Multivariate Predictors. *PLoS ONE* **2011**, *6*, e21896. [CrossRef] [PubMed]

169. Wee, C.-Y.; Yap, P.T.; Zhang, D.; Denny, K.; Browndyke, J.N.; Potter, G.G.; Welsh-Bohmer, K.A.; Wang, L.; Shen, D. Identification of MCI Individuals Using Structural and Functional Connectivity Networks. *NeuroImage* **2012**, *59*, 2045–2056. [CrossRef] [PubMed]

170. Kim, J.; Lee, J.-H. Integration of Structural and Functional Magnetic Resonance Imaging Improves Mild Cognitive Impairment Detection. *Magn. Reson. Imaging* **2013**, *31*, 718–732. [CrossRef] [PubMed]

171. Cui, Y.; Wen, W.; Lipnicki, D.M.; Beg, M.F.; Jin, J.S.; Luo, S.; Zhu, W.; Kochan, N.A.; Reppermund, S.; Zhuang, L.; et al. Automated Detection of Amnestic Mild Cognitive Impairment in Community-Dwelling Elderly Adults: a Combined Spatial Atrophy and White Matter Alteration Approach. *NeuroImage* **2012**, *59*, 1209–1217. [CrossRef] [PubMed]