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# Characterizing the Neurobiological Mechanisms of Action of Exercise and Cognitive–Behavioral Interventions for Rheumatoid Arthritis Fatigue: A Magnetic Resonance Imaging Brain Study

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**Objective.** Chronic fatigue is a major clinical unmet need among patients with rheumatoid arthritis (RA). Current therapies are limited to nonpharmacological interventions, such as personalized exercise programs (PEPs) and cognitive–behavioral approaches (CBAs); however, most patients still continue to report severe fatigue. To inform more effective therapies, we conducted a magnetic resonance imaging (MRI) brain study of PEPs and CBAs, nested within a randomized controlled trial (RCT), to identify their neurobiological mechanisms of fatigue reduction in RA.

**Methods.** A subgroup of patients with RA (n = 90), participating in an RCT of PEPs and CBAs for fatigue, undertook a multimodal MRI brain scan following randomization to either usual care (UC) alone or in addition to PEPs and CBAs and again after the intervention (six months). Brain regional volumetric, functional, and structural connectivity indices were curated and then computed employing a causal analysis framework. The primary outcome was fatigue improvement (Chalder fatigue scale).

**Results.** Several structural and functional connections were identified as mediators of fatigue improvement in both PEPs and CBAs compared to UC. PEPs had a more pronounced effect on functional connectivity than CBAs; however, structural connectivity between the left isthmus cingulate cortex (L-ICC) and left paracentral lobule (L-PCL) was shared, and the size of mediation effect ranked highly for both PEPs and CBAs ($ß_{Average}$ = −0.46, SD 0.61; $ß_{Average}$ = −0.32, SD 0.47, respectively).

**Conclusion.** The structural connection between the L-ICC and L-PCL appears to be a dominant mechanism for how both PEPs and CBAs reduce fatigue among patients with RA. This supports its potential as a substrate of fatigue neurobiology and a putative candidate for future targeting.

## INTRODUCTION

Fatigue is pervasive among people with inflammatory rheumatic diseases.[1] In patients with rheumatoid arthritis (RA), for example, 80% report significant fatigue[2] and over 70% consider this equal to pain in terms of burden.[3] Critically, most patients continue to experience severe fatigue despite successful anti-inflammatory treatment of their underlying disease.[4] This common scenario represents one of the principal challenges to face rheumatologists in routine practice. Management is currently limited to exercise and psychosocial interventions.[5] Although programs of these nonpharmacological therapies have been successfully implemented into rheumatology services,[6] their clinical effects are generally small to medium in size, with most recipients

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still reporting significant levels of fatigue. By understanding the mechanisms of fatigue reduction of these treatments, more effective interventions can be developed in the future.

Epidemiologic investigations implicate the importance of brain factors (eg, mental health) rather than with peripheral measures (eg, inflammation)[7] as a focus for putative fatigue mechanisms. Delineating in vivo human brain mechanisms is restricted by access to the brain; however, imaging offers a noninvasive surrogate approach. In patients with RA, and in patients with other chronic diseases, magnetic resonance imaging (MRI) modalities have identified multiple brain correlates of fatigue. These characterize the brain beyond what is achievable with conventional macroscopic clinical scans. They include volumetric morphometry, which enables quantification of regional volumes, cortical thickness, and surface areas; diffusion tensor imaging (DTI), which delineates white matter (WM) tracts and subsequent structural connectivity between different brain regions and functional connectivity MRI, an adaptation of functional MRI (fMRI) data that examines intrinsic connectivity. Together, these networks, or "connectomes," help map the communications between different brain regions. This is especially relevant in the context of complex behaviors, such as fatigue, the mechanisms of which are not likely constrained to a single region.

These MRI modalities have consistently associated fatigue to frontal, parietal, and cingulate cortices, alongside subcortical striatal structures.[8] In RA, higher fatigue levels were related to stronger functional connectivity between the dorsal attention network and bilateral prefrontal cortex as well as greater right putamen volumes.[9] Notably, MRI brain studies examining the neural effects of exercise and psychosocial interventions (eg, cognitive–behavioral approaches [CBAs]) have implicated similar regions.[10,11] Taken together, the neurobiological effects of exercise and psychosocial interventions plausibly modulate fatigue specific brain networks that represent the final common pathway of this heterogeneous symptom. Translational research can focus on probing major network hubs using noninvasive neuromodulation technologies as a basis for novel therapies. However, because of the diffuse nature of established neural correlates, it is uncertain which regions should be the focus for treatment. Moreover, the apparent variability, and often lack of reproducibility, of previously reported brain regions of interest (ROIs) may be attributable to suboptimal study designs.

Limitations of previous MRI brain fatigue studies include their cross-sectional or uncontrolled longitudinal design, preventing causal inferences. Clinical study designs applying mediation analysis via randomized controlled experiments are considered the gold standard in addressing this limitation.[12] Mediation analyses can examine why observed relations between variables exist or help understand outcomes associated with interventions to illuminate causal mechanism(s) through which variables relate.[13] The high dimensionality of neuroimaging data has previously precluded mediation analysis; however, advanced computational approaches have now enabled researchers to investigate the mechanism of action of exercise and CBA interventions with a view to deriving mechanistic insights into cognitive impairment.[14] Given their established benefit for fatigue, such interventions could be similarly leveraged, for the first time, to aid the selection and prioritization of putative neurobiological mediators of this patient priority.

This study is the first to embed multimodal MRI brain scans in a randomized controlled trial (RCT) of exercise and psychosocial therapies for RA fatigue. The parent trial evidenced statistically and clinically important fatigue improvements of both a telephone-delivered exercise and CBA intervention compared to usual care (UC). This MRI substudy aimed to employ mediation analyses to characterize the neurobiological mechanisms of action of these interventions and then rank the identified putative causal neural regions for future therapeutic targeting.

## PATIENTS AND METHODS

**Study design.** The study is a nested 3 Tesla MRI brain substudy within the Lessening the Impact of Fatigue Trial (LIFT).[15]

**Parent trial.** The LIFT was an RCT to test the hypothesis that UC with either telephone-delivered CBAs or a personalized exercise program (PEP) is more effective than UC (eg, a patient education booklet) alone. CBAs involved a structured psychological intervention, aiming to replace unhelpful beliefs/behaviors with adaptive ones. Alternatively, a PEP targeted intolerance of physical activity and reversal of deconditioning. In total, 368 patients with inflammatory rheumatic disease were randomized (patients with RA = 202). Participants randomized to an active arm received up to eight sessions lasting a maximum of one hour of therapy over a period of six months. The primary outcome was self-reported fatigue at 12 months (measured by the Chalder fatigue scale).[6] The study by Martin et al[15] contains further details of their characteristics and outcomes.

**MRI substudy.** *Inclusion criteria.* Patients must have been (a) ≥18 years, (b) consented to the parent trial randomization, (c) classified with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism criteria,[16] (d) fatigued longer than three months, (e) significantly fatigued (≥6 on the 1–10 visual analog scale), and (f) considered to have stable RA (as defined by unchanged immunomodulatory therapy in the previous three months).

*Exclusion criteria.* Patients were not considered if they had (a) alternative medical explanations for their fatigue (eg, anemia), (b) contraindications to MRI, and (c) already started an intervention. Recruitment processes have been previously reported.[6] Randomization was undertaken using a computer-generated sequence, participants were allocated to receive either of the two treatments or UC (1:1:1 ratio). Those eligible were provided information on the substudy, and following randomization, they were offered an appointment to attend an MRI research facility

within a month (and before their first telephone consultation if they receive active therapy).

*Clinical assessment.* All patients were comprehensively characterized at baseline and at six months as part of the parent trial. This included disease activity, C-reactive protein, disease duration, and comorbidities (Charlson index).[1]

**MRI imaging parameters.** MRI multimodal data were acquired in three scanning sites with two system types: a 3 Tesla Philips Achieva X-series (Philips) and a 3 Tesla Siemens Prisma (Siemens) using 32 channel phased-array head coils. All patients consented before scanning. The multimodal scanning consisted of the following.

*Structural MRI.* Structural MRI data were acquired by a T1-weighted magnetization-prepared rapid acquisition gradient-echo/fast-field echo three-dimensional structural scan with the following parameters: repetition time (TR) = 8.2 ms, echo time (TE) = 3.8 ms, inversion time = 1,025.7 ms, flip angle (FA) = 8°, field of view (FOV) = 240 × 240 mm, matrix size = 240 × 240 with 160 sagittal slices, voxel size = 1 × 1 × 1 $mm^3$, and total scan time = 5.63 minutes.

*Resting-state fMRI.* Resting-state fMRI data were collected with a T2*-weighted, gradient-echo, echo-planar imaging (EPI) pulse sequence with the following parameters: TR = 1.95 s, TE = 26 ms, FA = 70°, FOV = 240 × 240 mm, matrix size = 128 × 128 with 30 transverse slices in ascending order, voxel size = 1.88 × 1.88 × 3.5 $mm^3$ with slice gap = 1.5 mm, 308 volumes, and total scan time = 10.01 min. Patients were instructed to keep their eyes open during the scan and focus on a displayed fixation cross.

*Diffusion MRI.* Diffusion MRI was acquired using a single-shot, spin-echo EPI sequence with the following parameters: TR = 7,010 ms, TE = 90 ms, FA = 90°, FOV = 220 × 220 mm, matrix size = 96 × 96 with 60 transverse slices, voxel size = 2.3 × 2.3 × 2.3 $mm^3$ with no gap, one excitation, gradient directions = 64 (b = 2000 s/$mm^2$), and eight volumes of unweighted (b = 0) images.

**MRI data preprocessing.** *Structural MRI.* All the structural data were preprocessed using FreeSurfer image analysis suite version 6.0 (http://surfer.nmr.mgh.harvard.edu/). The preprocessing pipelines includes skull stripping motion correction, intensity normalization, Talairach registration, skull stripping, subcortical segmentation and labeling, segmentation of WM, tessellation of the gray matter (GM)/WM and GM/cerebrospinal fluid boundaries, automated topology correction, surface deformation, and cortical surface reconstruction.[17] Each individual's brain was parcellated into 84 cortical and subcortical ROIs (42 ROIs per hemisphere). Surface area, cortical thickness, and volume measures were extracted from each individual's ROI.

*Resting-state fMRI.* All the resting-state fMRI data were preprocessed using CONN functional connectivity toolbox, a MATLAB-based cross-platform software for preprocessing and analyzing MRI functional connectivity. The default surface-based, subject-space analyses pipeline was used. Briefly, the analysis pipeline consists of motion correction, slice-time correction, outlier detection (scrubbing) using Artifact Detection Tools (ART) toolbox, coregistration to the structural volume, smoothing (8-mm full width at half maximum kernel), denoising, nuisance regression (principal components of WM and CSF, mean GM signal, six rigid-body realignment movement covariates, and scrubbing series), linear detrending, and band-pass filtering (0.008–0.09 Hz). Functional connectivity ROI–ROI connectivity was computed using 84 cortical and subcortical ROIs, and an 84 × 84 symmetrical Fisher Z-transformed matrix (FC) was estimated using ROI blood oxygen level–dependent signals of each patient.

Diffusion MRI: All the diffusion data were preprocessed using FMRIB Software Library (FSL version 6.0 and FSL Diffusion Toolbox). The preprocessing procedures include skull stripping, eddy current distortion correction, motion correction, fractional anisotropy calculation, probabilistic distributions estimation using the graphics processing unit version of BEDPOSTX tool,[18] and, finally, performing the probabilistic tractography to estimate the structural connectivity probability among 84 cortical and subcortical regions using the PROBTRACKS tool,[19] which yields an 84 × 84 asymmetric structural connectivity matrix for each patient. After preprocessing, all the MRI features from the three treatment subgroups were merged, and the difference (Δ) between the two sessions was calculated, and a multimodal matrix (ΔMM) was created by horizontally concatenating the above ΔMRI matrices, forming a matrix of ($N_{subj}$ × $10{,}678_{features}$).

**The mediation analysis.** An agnostic multigroup, multimediator mediation analysis was implemented to explore how brain imaging features mediate the relationship between fatigue improvement and each of the two intervention groups (relative to control). We examined the neural variables of fatigue, which are not necessarily causing fatigue. Nevertheless, inferences for the two concepts are statistically identical.[20,21] The mediators are neural/brain imaging features that can be used to describe the relationship between the interventions (the independent/exposure variable) and fatigue improvement (the dependent variable/outcome; Figure 1). The analysis investigates the indirect effect carried by individual mediators separately and was implemented using the *mmabig* package in statistics software R.[24]

The outcome (Y) is Chalder fatigue score improvement over time. The predictor (exposure variable, X) is the intervention group, a (multi-)categorical variable of the values of 1 or 2 or 3. Group 2 (reference group) is the UC receivers. The analysis was blinded to the two intervention groups (PEPs and CBAs). The potential mediators are the neural/brain imaging features. We calculated the difference between the values of the features for session 1 subtracted from the corresponding values for session 2. Furthermore, five different variables as covariates (exogenous variables) were included in the analysis. The covariates

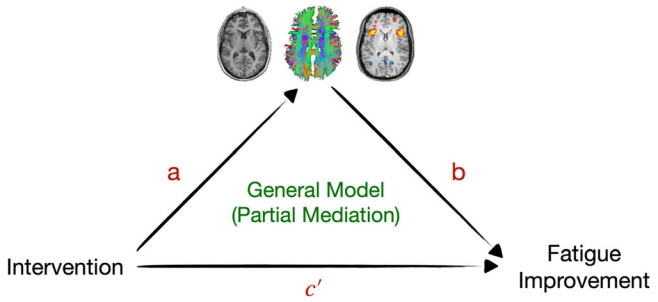


**Figure 1.** The general mediation model for this study. The brain imaging measures are tested for mediation in fatigue improvement in different intervention groups. The indirect effect is the product of the a and b path coefficients, which measures the changes in the dependent variable when the independent variable is fixed and the mediator variable changes (by the amount that it would have changed if the independent variable increased by one unit). The direct effect is denoted as c' and measures the changes in the independent variable when the dependent variable increases by one unit (the mediator variable remains unchanged).[22,23]

consisted of Chalder fatigue score for session 1, age at session 1, total brain volume for session 1, study center, and gender. A generalized linear model was used for modeling the relationship among the variables that were included in the mediation analysis and the response. The linkage function was set to gaussian (link equals "identity").[22] The regression technique that was used in this research is the least absolute shrinkage and selection operator (Lasso) (Supplementary Methods). A bootstrapping step with 1,000 iterations was implemented to determine the uncertainty in the estimation of the mediation effects for each model. The mean, SD, and confidence intervals values of the bootstrapped samples from the estimates were calculated and tested to identify the significant mediators. Indeed, the bootstrapping followed the design of the study (eg, each treatment group was bootstrapped separately). The procedure was repeated for all the five different combinations of the modalities to complete our agnostic technique to explore the pathways. The results were further adjusted for multiple comparisons using the Bonferroni correction technique (Supplementary Methods for further statistical information).

**Data availability and ethics approval.** Anonymized individual patient data will be made available following any reasonable request made to the corresponding author, subject to a data-sharing agreement and UK research governance regulations. The intervention manuals can be found on https://www.abdn.ac.uk/iahs/research/epidemiology/lift-1286.php.

All the details of the parent trial are published/included in *BMJ Open* paper doi:10.1136/bmjopen-2018-026793.

## RESULTS

In total, 90 patients gave consent and were randomized to each treatment arm, two of which did not complete a baseline MRI scan. After six months, complete fatigue follow-up, T1, resting state, and DTI scans were available for n = 67 (Table 1; Supplementary Methods for further clinical variables).

**Multimodal MRI data curation.** A combination of features was extracted from five different modalities of the original raw data: (a) a total number of 84 volumetric features (values) were extracted from the MRI structural data. (b) A total of 68 area features (values) and (c) 68 thickness features (values) were extracted from the MRI structural data. (d) A total of 3,486 resting-state functional connectivity features were extracted from the connectivity matrices of the rs-fMRI data. These matrices are diagonal (ie, the relationship between one brain region and the other is the same regardless of the direction). And (e) 6,972 structural connectivity features were extracted as from the connectivity matrices of the diffusion data.

**PEP mediation analysis.** There were 17 structural and 13 functional connections identified as the mediators for fatigue changes for the PEP intervention group as compared to the UC group, being the reference group (Figure 2; Supplementary Methods). There were no mediators identified for the volumetric metrics. The strongest structural connectivity mediators were left isthmus cingulate cortex (L-ICC) to left paracentral lobule (L-PCL) with a mean ± SD mediation effect of –46 ± 0.61, left pars orbitalis to right paracentral with a mean ± SD mediation effect of –0.29 ± 0.53, and the left lateral occipital gyrus to left cuneus with a mean ± SD mediation effect of –0.24 ± 0.4. In terms of functional connectivity, the most significant mediators were the connections between left accumbens and right rostral anterior cingulate with a mean ± SD mediation effect of –0.62 ± 0.61, the connection between left pallidum and right superior parietal lobule with a mean ± SD mediation effect of –0.41 ± 0.5, and the connection between left pallidum and left inferior temporal gyrus with a mean ± SD mediation effect of –0.39 ± 0.51.

**CBA mediation analysis.** A total of 17 structural and 12 functional connections were identified as mediators for CBA-related fatigue change, relative to the UC group (Figure 3; Supplementary Methods). No mediators were identified for the volumetric modalities (volume, thickness, and area). The strongest mediators for the structural connections were left pars triangularis to left putamen with a mean ± SD mediation effect of –0.32 ± 0.47, L-ICC to L-PCL with $ß_{Average}$ = -0.31 ± 0.54, and the left accumbens to left transverse temporal gyrus with $ß_{Average}$ = -0·24 ± 0.38. Although significant functional connections were identified, their size of effect was minimal. The location of the most significant mediating connections, with an absolute effect size of above 0.1, for each intervention can be seen in Figure 4.

**Table 1.** Clinical characteristics of all the intervention/treatment group patients*

| Characteristics | CBA (n = 21) | PEP (n = 24) | UC (n = 22) | Total (n = 67) |
|---|---|---|---|---|
| Gender, n (%) | | | | |
| Female | 14 (66.7) | 19 (79.2) | 18 (81.8) | 51 (77.3) |
| Male | 7 (33.3) | 5 (20.8) | 4 (18.2) | 16 (22.8) |
| Age, y | 62 (13) | 58 (13) | 58 (10) | 59 (12) |
| Imaging site, n (%) | | | | |
| Aberdeen | 11 (52.4) | 16 (667) | 17 (77.3) | 44 (65.7) |
| Edinburgh | 10 (47.6) | 6 (25) | 5 (22.7) | 21 (31.3) |
| Glasgow | 0 | 2 (8.3) | 0 | 2 (3) |
| Disease duration, y | | | | |
| Mean ± SD | 11.30 ± 9.01 | 11.29 ± 10.55 | 12.06 ± 10 | 12.39 ± 10.39 |
| Median | 8.44 | 8.86 | 9.75 | 9.37 |
| IQR | 12.07 | 8.82 | 11.10 | 12.95 |
| Skewness | 0.86 | 1.07 | 1.40 | 1.06 |
| Kurtosis | 2.71 | 3.12 | 4.62 | 3.17 |
| Medication change (new or increase) | 1; $X^2$ (1.21) = 0.82 | 3; $X^2$ (1.24) = 0.64 | 2; $X^2$ (1.22) = 0.71 | 6; $X^2$ (1,67) = 0.75 |
| Baseline comorbidity index (number of patients)[a] | | | | |
| 1 | 9 | 16 | 13 | 38 |
| 2 | 6 | 7 | 8 | 21 |
| 3 | 3 | 1 | 1 | 5 |
| 4 | 2 | 0 | 0 | 2 |
| 7 | 1 | 0 | 0 | 1 |
| RA disease activity[b] baseline | 4.5 (0.90) | 4.1 (1.1) | 3.6 (1.1) | 4.1 (1.1) |
| RA disease activity six months | 4.2 (0.97) | 4.2 (1.4) | 3.5 (1.2) | 4.0 (1.2) |
| CRP baseline, mg/L | | | | |
| Mean ± SD | 7.11 ± 7.06 | 7.84 ± 9.41 | 4.14 ± 2.46 | 6.22 ± 6.76 |
| Median | 4 | 4 | 4 | 4 |
| IQR | 4 | 4.25 | 0 | 1.75 |
| Skewness | 2.97 | 2.12 | 1.65 | 3.20 |
| Kurtosis | 12.70 | 7.12 | 6.66 | 14.76 |
| CRP six months, mg/L | | | | |
| Mean ± SD | 10.50 ± 13.02 | 6.16 ± 6.36 | 6.89 ± 16.36 | 6.80 ± 8.80 |
| Median | 4 | 4 | 4 | 4 |
| IQR | 8 | 2 | 1.75 | 2 |
| Skewness | 2.28 | 2.17 | 4.76 | 3.48 |
| Kurtosis | 7.61 | 6.77 | 24.13 | 16.70 |
| Chalder fatigue baseline, mean ± SD | 20 ± 6.8 | 21 ± 6.0 | 21 ± 4.6 | 21 ± 5.8 |
| Chalder fatigue six months | | | | |
| Mean ± SD | 13.62 ± 7.17 | 14 ± 7.3 | 19 ± 5.7 | 15 ± 6.8 |
| Median | 15 | 15 | 15 | 15 |
| IQR | 7.50 | 7.50 | 7.50 | 7.50 |
| Skewness | 0.16 | 0.16 | 0.16 | 0.16 |
| Kurtosis | 2.51 | 2.51 | 2.51 | 2.51 |

* The skewness values for the variables that have a mean ± SD <2 are also reported. CBA, cognitive–behavioral approach; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; IQR, interquartile range; PEP, personalized exercise program; RA, rheumatoid arthritis; UC, usual care.
[a] Charlson comorbidity index score.
[b] DAS28 score.

## DISCUSSION

In this study, the first to investigate how exercise and psychosocial interventions alter the brain to improve RA-related fatigue, we have identified multiple WM structural and functional brain connections that potentially mediated fatigue change. In contrast, individual brain structure volumetrics did not appear to have a causal role in symptom improvement.

Regarding structural connectivity, the effect of exercise on fatigue improvement was principally mediated by the WM connection between the L-ICC and L-PCL. Notably, this specific feature was also a highly ranked mediator of the CBA intervention. This highlights the potential of this connection as a final common neurobiological substrate of fatigue, which both interventions appear to have successfully targeted. Although this is the first study to examine WM connectivity in the context of RA fatigue mechanisms, we and others have previously employed DTI and similarly identified the isthmus cingulate cortex (ICC) as a feature of fatigue in other inflammatory rheumatic diseases.[27,28] Its role

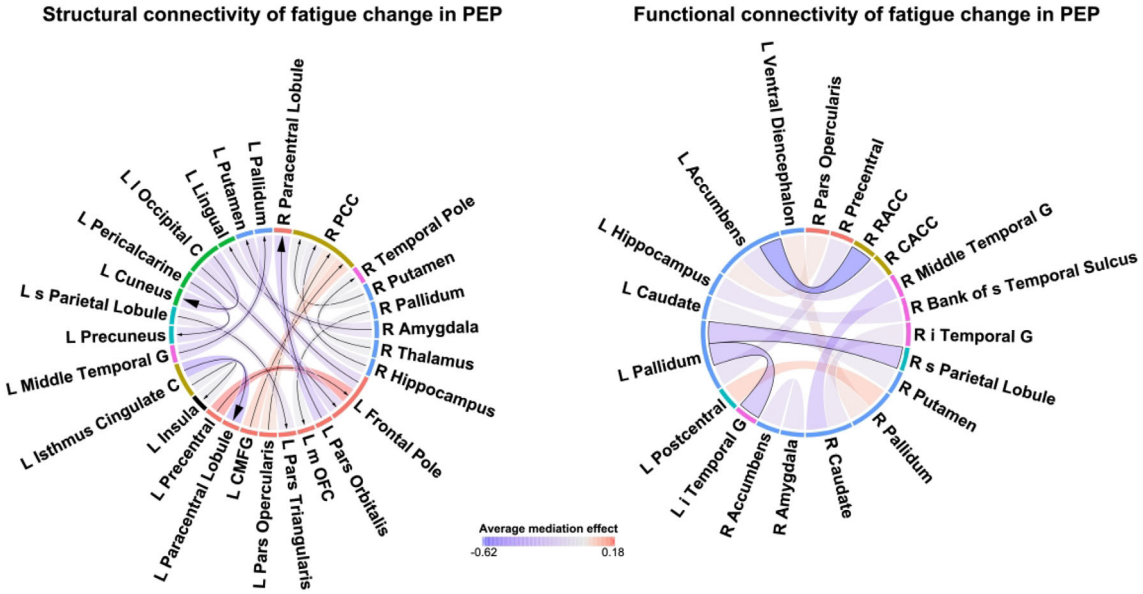


**Figure 2.** (a) A total of 17 structural connectivity features/connections (left) and (b) 13 functional connectivity features/connections (right) were identified as the mediators for the fatigue changes in the PEP intervention group, with the usual care group as the reference group in the analysis. The color metric illustrates the average of the estimation of mediation effects from bootstrap samples (a total of 1,000 iterations), which ranges from –0.62 to 0.18. The three strongest mediators are illustrated by bigger arrow heads and solid borders for structural connectivity and functional connectivity, respectively. The figure was created using Circlize toolbox[25] CACC, caudal anterior cingulate cortex; CMFG, caudal middle frontal gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PEP, personalized exercise program; RACC, rostral anterior cingulate cortex.

as a hub of the default mode network (DMN) may be highly relevant. DMN activity indicates introspective behavior that may empower cognitive functions but with overuse could lead to fatigue. Not only are such cognitions a common target of CBAs, but in parallel, there is now extensive structural and fMRI data evidencing a modulatory effect of exercise upon the DMN.[29] The

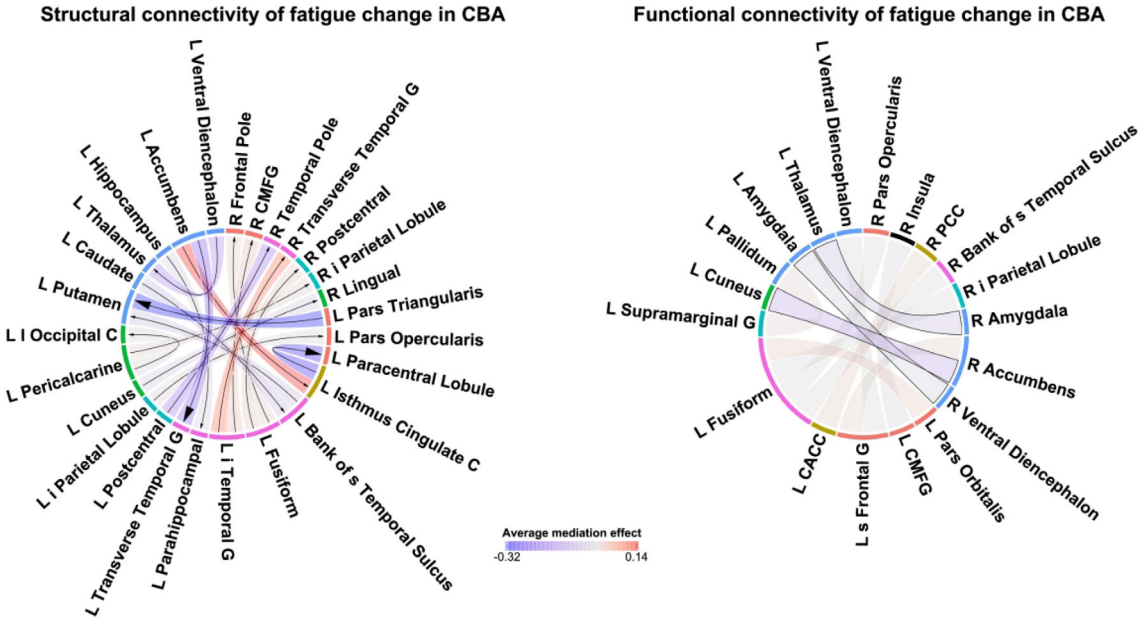


**Figure 3.** (Left) A total of 17 structural connectivity features/connections and (right) 12 functional connectivity features/connections were identified as the mediators for the fatigue changes in the CBA intervention group, with the usual care group as the reference group in the analysis. The color metric illustrates the average estimation of mediation effects from bootstrap samples (a total of 1,000 iterations), which ranges from –0.32 to 0.14. The three strongest mediators are illustrated by larger arrow heads and solid borders for structural connectivity and functional connectivity, respectively. The figure was created using Circlize toolbox.[25] C, cortex; CACC, caudal anterior cingulate cortex; CBA, cognitive–behavioral approach; CMFG, caudal middle frontal gyrus; G, gyrus; i, inferior; L, left; l, lateral; m, medial; PCC, posterior cingulate cortex; R, right; s, superior.

paracentral lobule (PCL) is also a key hub of the somatosensory network (SMN), which was structurally related to fatigue in ankylosing spondylitis.[28] We therefore hypothesize that the connection between these regions do not mediate fatigue improvement in isolation; rather, we hypothesize that they bridge and bring the effect of these greater networks.

It is notable that both the DMN and SMN are critical networks in pain processing, and a systematic literature review identified pain as one of the strongest predictors of RA fatigue.[30] We have further showed that, unlike other common predictors, pain clustered with fatigue across almost all patients.[31] Thus, it is unsurprising that fatigue and pain appear to share neurobiological mechanisms, a hypothesis further supported by the known effectiveness of PEPs and CBAs in chronic pain conditions.[32] Given the diverse natures of PEPs and CBAs, it may be perceived unusual that the ICC-PCL structural connection appears an important mechanism for both interventions. However, we know from the parent trial that many CBA recipients felt better able to increase their exercise levels once some of their cognitive challenges were addressed. There were no other neurobiological mediators shared between the interventions.

Overall, the neurobiological functional effect of PEPs on fatigue closely resembled our previous cross-sectional, fMRI-based RA fatigue correlate findings,[9] which strongly implicated overactivity of the dorsal attention network. In the current study, a PEP appears to reduce the functional activity of connections involving the superior parietal lobule, middle temple gyrus, and precentral regions (all landmarks of the dorsal attention network) with subsequent reductions in fatigue. Structural dysconnectivity of the precentral regions was also observed following PEPs. More generally, across both interventions and MRI metrics, regions of the basal ganglia (pallidium, putamen, accumbens, and caudate) were commonly identified, aligning with the canonical Chaudhuri and Behan model of chronic fatigue.[33,34] This was originally framed on neurologic observations of patients with lesions of the basal ganglia and their connections, especially Parkinson disease, in which fatigue is indeed considered a primary manifestation.[35] It is important to recognize that the identified candidate connections do not explain the totality of fatigue neural processing. The complexity of fatigue inevitably means that it will be underpinned by multiple regions/

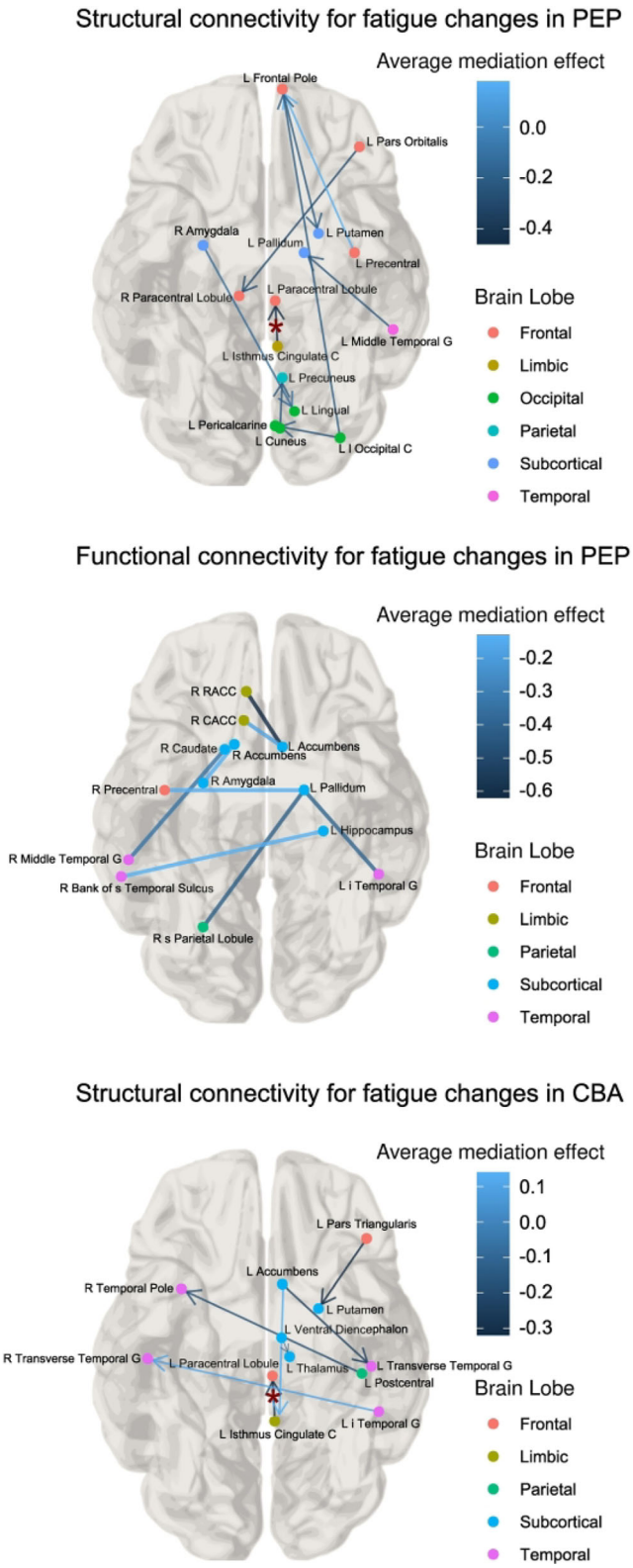


**Figure 4.** (Top) The location of the most significant structural connectivity features/connections and (middle) the location of the most significant functional connectivity features/connections that were identified as mediators for fatigue change in the PEP intervention group. (Bottom) The location of the most significant structural connectivity features/connections (bottom) that were identified as mediators for fatigue changes in the CBA intervention group. The color metric illustrates the average of the estimation of mediation effects from bootstrap samples (a total of 1,000 iterations), which only includes the absolute values above 0.1. The figure was created using the brainconn software package.[26] C, cortex; CACC, caudal anterior cingulate cortex; CBA, cognitive–behavioral approach; G, gyrus; i, inferior; L, left/lobule; l, lateral; m, medial; PEP, personalized exercise program; R, right; RACC, rostral anterior cingulate cortex; s, superior.

networks; however, our identified candidate connections represent critical components of the more expansive fatigue network and provide a focus for interventions.

One limitation of the present study was the inability to externally validate our findings because, to the best of our knowledge, there are no past or current randomized controlled clinical trials of RA with embedded multimodal MRI brain imaging. However, our findings are biologically plausible and have externally validated and prioritized neural correlates identified in previous studies.[8,9] Secondly, our study did not identify volumetric features despite previous cross-sectional research highlighting their potential importance. This is potentially because of the longer timescale needed for volumetric changes to occur or be a consequence of differences in statistical power for these metrics, not withstanding that this is the largest MRI brain study to date of any inflammatory rheumatic disease. Third, this study lacks alternative disease comparators, and so, although the highlighted brain regions have been consistently identified in other clinical populations, we are unable to confidently establish the transferability of these findings to other disease states. Fourth, there is the risk of residual confounding from unmeasured factors. However, variables such as inflammation and disease activity did not alter significantly during follow-up, and regardless, RA fatigue is established as a multidimensional construct,[36] which comprises such variables and thus correcting for them removes elements that represent the essence of our symptom of interest. Finally, structural connectivity could be expected to provide an anatomic basis for function, but in this study, the overlap between the identified structural and functional connectivity mediators was small. However, a direct, spatially aligned relationship is not always observed in other combined functional and structural connectivity MRI studies; rather, in the context of pathology, a more indirect relationship is proposed in which the quality of the structural connectivity moderates functional activity.[37]

Despite these shortcomings, this study discloses multiple novel routes for potential fatigue therapeutics. Neuromodulation techniques could noninvasively target identified regions using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). These techniques affect regional brain functional and structural connectivity[38,39] through magnetic field–inducing coils or scalp electrodes, respectively, and in severe depression, their application to brain frontal regions is already established in routine clinical care.[40] However, stimulation range limits TMS/tDCS targets to accessible regions on the surface of the brain and so precluding optimal modulation of our strongest candidate, the ICC-PCL WM connection. Instead, the emerging application of transcranial pulse stimulation could overcome this limitation. Further, real-time neurofeedback paradigms could address functional targets by training patients to alleviate aberrant connectivity and potentially reduce subsequent fatigue.[41]

Understanding and managing fatigue presents one of the most sizable contemporary challenges in the care of patients with RA. Employing a gold-standard causal analysis framework, this study examined the neurobiological mechanisms of action of two effective nonpharmacological RA fatigue interventions and, in doing so, identified and prioritized candidate brain substrates of RA fatigue that can now be targeted directly with a view to developing novel solutions for this unmet clinical need.

Chronic fatigue is a major clinical unmet need among patients with RA. Current therapies are limited to nonpharmacological interventions, such as PEPs and CBAs; however, most patients still continue to report severe fatigue.

Employing a gold-standard causal analysis framework, this study examined the neurobiological mechanisms of action of two effective nonpharmacological RA fatigue interventions. To inform more effective therapies, we conducted an MRI brain study of PEPs and CBAs, nested within an RCT, to identify their neurobiological mechanisms of fatigue reduction in RA.

The structural connection between the L-ICC and L-PCL appears to be a dominant mechanism for how both PEPs and CBAs reduce fatigue among patients with RA. This supports its potential as a substrate of fatigue neurobiology and a putative candidate for future targeting.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Dehsarvi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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