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ORIGINAL RESEARCH

Brain structural connectomes indicate shared neural circuitry involved in subjective experience of cognitive and physical fatigue in older adults

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Abstract

Cumulative evidence suggests the existence of common processes underlying subjective experience of cognitive and physical fatigue. However, mechanistic understanding of the brain structural connections underlying the experience of fatigue in general, without the influence of clinical conditions, is limited. The purpose of the study was to examine the relationship between structural connectivity and perceived state fatigue in older adults. We enrolled cognitively and physically healthy older individuals ($n = 52$) and categorized them into three groups (low cognitive/low physical fatigue; low cognitive/high physical fatigue; high cognitive/low physical fatigue; no subjects had high cognitive/high physical fatigue) based on perceived fatigue from cognitive and physical fatigue manipulation tasks. Using sophisticated diffusion tensor imaging processing techniques, we extracted connectome matrices for six different characteristics of whole-brain structural connections for each subject. Tensor network principal component analysis was used to examine group differences in these connectome matrices, and extract principal brain networks for each group. Connected surface area of principal brain networks differentiated the two high fatigue groups from the low cognitive/physical fatigue group (high vs. low physical fatigue, $p = 0.046$; high vs. low cognitive fatigue, $p = 0.036$). Greater connected surface area within striatal-frontal-parietal networks was correlated with lower cognitive and physical fatigue, and was predictive of perceived physical and cognitive fatigue measures not used for group categorization (Pittsburgh fatigability physical subscale, $R^2 = 0.70$, $p < 0.0001$; difference in self-report fatigue before and after gambling tasks, $R^2 = 0.54$, $p < 0.0001$). There are potentially structural connectomes resilient to both cognitive and physical fatigue in older adults.

Keywords Diffusion tensor imaging · Connectome · Cognitive fatigue · Physical fatigue · Principal component analysis

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Abbreviations

CF	cognitive fatigue
DTI	diffusion tensor imaging
FA	fractional anisotropy
MD	mean diffusivity
PC	principal component
PF	physical fatigue
ROI	region of interest
RPE	rating of perceived exertion
TN-PCA	tensor network principal component analysis

Introduction

Fatigue is among the most common symptom complaints in aging, as well as numerous chronic diseases(Swain 2000), and has major consequences on impairing cognitive and motor function (K. Avlund et al. 2003; Gill et al. 2001; Simonsick et al. 2016). While cognitive fatigue (CF) and physical fatigue (PF) both influence performance in their respective domains (Boksem et al. 2005; Mackworth 1964; Tanaka and Watanabe 2012), CF can also affect physical performance, and PF can also affect cognitive performance. Individuals who easily experience CF exhibit a decline in endurance performance (Van Cutsem et al. 2017) and perceive more effort in response to exercise (Marcora et al. 2009). Exhaustion from intensive or prolonged physical exercise has been shown to compromise cognitive function (Tomporowski 2003). This cumulative evidence suggests that there may be some common processes underlying the experience of, or resilience to, fatigue irrespective of the type of fatigue manipulation task.

Cognitive and physical fatigue can be assessed both objectively, through quantitative measures of performance, and subjectively, through self-report. Objective observations of fatigue are typically referred to as performance fatigability, while subjective reports are typically referred to as perception of fatigue(B. M. Kluger et al. 2013). While it would seem that these phenomena should be related, multiple studies have found limited correlation between subjective perception of fatigue and performance fatigability across both healthy subjects and multiple disease processes (Bailey et al. 2007; Cockshell and Mathias 2014; Jarad et al. 2012). Further, perceived fatigue has been shown to be predictive of future disability outcomes(Kirsten Avlund et al. 2002; Juengst et al. 2013). Here, we therefore focus on the perception of fatigue, referred to simply as "fatigue" throughout.

The common definition of fatigue relies on subjective lack of physical and/or mental energy following cognitive or physical tasks with extended demands on sustained effort (Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis 1998). Following cognitive fatigue (CF) manipulation tasks such as the Nback and Stroop tasks, subjects have significantly increased subjective ratings of fatigue (Klaassen et al. 2016; Lin et al. 2013). Physical fatigue (PF) manipulation tasks, such as repeated motor tasks or extended physical exercise, have been shown to increase perceived energy deprivation (Schaaf et al. 2018). These task-induced changes in fatigue are known as state fatigue, as opposed to trait fatigue, which is related to chronic conditions. Compared to trait fatigue, state fatigue is common in older adults in general, with a major impact on their functional health, and is potentially modifiable (Eldadah 2010). Understanding the mechanisms underlying resilience to state fatigue, especially across multiple types, would facilitate the development of effective intervention strategies.

Neurobiological factors are crucial in contributing to perception of fatigue that is induced by cognitive or physical efforts (B. M. Kluger et al. 2013). There are a few categories of brain areas where functional changes are seen when fatigue is explicitly perceived: regions involved in motivation and goal setting, such as the insular, prefrontal, and anterior cingulate cortices (Klaassen et al. 2016; Muller and Apps 2018), and regions involving attention, processing speed, and motor function within frontal-striatal networks (Calabrese et al. 2010; Cook et al. 2007). Links have been found between perception of fatigue and white matter changes in patients with multiple sclerosis (Bester et al. 2013), chronic fatigue syndrome (Puri et al. 2012), and Gulf war illness (Rayhan et al. 2013). However, there has been inconsistency in the implicated white matter tracts and their respective regions. It is unclear whether these are mechanisms specific to clinical conditions or the experience of fatigue in general, as most previous studies examined white matter changes in the context of chronic fatigue. It also remains to be seen whether a more mechanistic understanding can be applied to examine why fatigue, regardless of type, is so common in aging populations and why some individuals do not experience this fatigue. Given the cumulative literature showing the importance of white matter tracts in supporting brain function, we hypothesize that there exists a structural connectivity signature for general resilience to state fatigue in aging.

To test this hypothesis, we examined state fatigue derived from intensive or prolonged cognitive and physical tasks on a group of healthy older adults without cognitive, behavioral, neurological, or psychiatric complications, and conducted diffusion tensor imaging (DTI) to investigate the role of white matter tracts. We used advanced DTI processing and statistical tools to examine the relationship between multiple metrics of structural connectomes and cognitive and physical state fatigue.

Methods and materials

Participants

Fifty-two older adults with normal cognition (indexed by Montreal Cognitive Assessment ≥26 and Rey Auditory

Verbal Learning Test delayed recall ≥6) were recruited for this study (mean age = 71 ± 5.12, 69.2% female, years of education = 17 ± 2.81). Inclusion criteria included: (1) capacity to give consent (indexed by UCSD Brief Assessment of Capacity to Consent), (2) free from major depression (indexed by Geriatric Depression Scale 15-item score < 6), sleep disorders (indexed by Pittsburgh Sleep Quality Inventory global sleep quality score < 14), chronic fatigue (indexed by 20-item Multidimensional Fatigue Inventory general fatigue subscale <20), (3) ≥60 years of age, (4) English-speaking, community-dwelling. Exclusion criteria included: (1) potential disease or medication confounded with fatigue symptoms, (2) neurologic or vascular disorders, (3) episode of diagnosed and active psychiatric disorder within past five years, (4) schizophrenia, (5) clinical diagnosis of mild cognitive impairment or dementia, (6) change in medication or beta-blocker dosage within past three months, and (7) MRI contraindications. Individuals with chronic fatigue were excluded in order to eliminate the confounding effects of trait fatigue on the analysis of mechanisms related to state fatigue. The study and all procedures were approved by the local Institutional Review Board. All participants provided written consent.

Study design

Subjects participated in four study visits, each two weeks apart, with the first two focused on physical fatigue and the second two focused on cognitive fatigue. Each fatigue measure was performed at a separate study visit in order to avoid the influence of prior tasks on performance in subsequent tasks. The Pittsburgh fatigability scale-physical questionnaire was administered at the initial screening visit, while a 6-min walking test was administered at the second visit. CF-manipulation tasks were performed at the final two visits, and consisted of either 2 executive function or gambling tasks, with each task type done at a separate visit. The order of the CF-manipulation task visits was randomized, and the order of the tasks within the same type was randomized within visit. During the study visits related to CF measures, we also conducted MR imaging (DTI and T1-weighted imaging) prior to the CF-manipulation tasks. Imaging protocols are described in detail below.

Fatigue measures and grouping

The two PF measures were the perceived fatigability severity derived from a 6-min walking test and the Pittsburgh fatigability scale-physical questionnaire. Prior to starting the walking test, participants rated their current level of perceived exertion using the Borg Rating of Perceived Exertion (RPE) scale (Borg 1982). Participants were then instructed to walk back and forth down a 50 ft hallway as quickly as possible but at a pace that could be maintained for 6 min. The time at which the participant completed each lap was recorded, as well as the participant's position at the end of the 6 min. Immediately following the walking test, participants rated their current level of perceived exertion once more using the Borg RPE scale. Physical fatigue was assessed using the Borg RPE before and immediately after the physical fatigue procedure. The Borg RPE scale ranges from 6 ("No exertion") to 20 ("Maximal Exertion"). Subjects were shown a visualization of the scale and asked to indicate the number that best described how they felt at that moment. The primary measure of physical state fatigue was perceived fatigability severity, which was calculated by dividing change in Borg RPE by total distance walked (Schnelle et al. 2012).

The Pittsburgh fatigability scale-physical questionnaire (Glynn et al. 2015) was used as a validation measure. This asked subjects to rate the physical fatigue they would expect to feel following ten common activities from 0 ("No fatigue") to 5 ("Extreme fatigue"), with the final score obtained by summing across all questions (score range 0–50). We consider this to be an independent measure of state fatigue, since the Pittsburgh fatigability scale is closely associated with both perceived exertion and performance following a walking task (Glynn et al. 2015). Of note, perceived fatigability severity and Pittsburgh fatigability score were significantly correlated across all subjects (Pearson's r = 0.49, $p = 0.0002$).

To induce cognitive fatigue, participants completed two computerized cognitive tasks at each visit, with each task lasting for 15 min. Since reduced motivation and increased mental effort are two of the major mechanisms related to CF (Dobryakova et al. 2013), the cognitive tasks included two commonly used executive function or gambling tasks at each visit in order to measure mental effort and motivation, respectively. Tasks within a given visit were performed consecutively, with no break between tasks. The two executive function tasks were Stroop Color Word (inhibitory control) and Dual 1-back (working memory). For the Stroop task, participants were shown serial colored words on the screen, and asked to judge the color of the word regardless of the meaning of the word as quickly and accurately as possible. Stroop trials began with a 0.5 s fixation period (white dot) and a 3 s stimulus interval, followed by 4 s response window and a 1.5 s feedback display ("correct" or "incorrect"), for a total duration of 9 s. The inter-stimulus interval lasted 3 s, and the probability of a given name-font condition was set at 0.25. For the Dual 1-back task, participants were shown an English letter on the screen, and asked to judge if the current stimulus matched the letter and position of the previous one as quickly and accurately as possible. Each trial consisted of a 0.5 s fixation period (white dot), a 2 s stimulus interval, a 5 s response window, and a 1.5 s feedback display ("correct" or "incorrect"), for a total duration of 12.5 s. The inter-stimulus interval lasted 5 s, and the probability of a positive "match" trial was set at 0.65. These tasks have been

shown to induce reduction of cognitive performance in those reporting high cognitive fatigue (Ren et al. 2019).

The two gambling tasks were the Iowa gambling task and balloon analog risk. For the Iowa gambling task, participants were presented with four virtual decks of cards, A, B, C, and D, and were asked to select cards in order to maximize profit. Each time participants chose a card, a specified amount of money would be awarded, but sometimes there would be a penalty instead. They had to choose between decks that would yield a high immediate gain but larger future losses (A & B, i.e., bad deck) and decks that would yield a low immediate gain but smaller future losses (C & D, i.e., good deck). Each trial consisted of a 0.1 s visual cue that highlighted the active deck, a 4 s response window, and a 2 s feedback display (amount of money), for a total duration of 6 s. The inter-stimulus interval was set at 3 s. For the balloon analog risk task, participants were presented with "balloons" on a screen and given the opportunity to "pump" the balloon to earn monetary rewards. When the balloon became larger, it would increase participant income, but also the probability of 'popping' the balloon and losing income. Participants were instructed to maximize income in each trial while avoiding losses. Each trial consisted of a 2 s fixation, a 3 s initial response window, during which participants were required to begin inflating the balloon, and a 2 s feedback display (indicating an explosion or a deposit), for a total of 7 s. The inter-stimulus interval was set at 3 s.

An adapted 18-item visual analog scale (Lee et al. 1991) was administered before and immediately after executive function or gambling tasks, modified to use a Likert scale ranging from 0 ("not at all") to 10 ("very much") rather than visual analog lines (Lin et al. 2016). Participants were instructed to rate their current state based on terms related to mood and energy (e.g. tired, keeping your eyes open is difficult, lively, efficient) by marking an 'X' in a box below the corresponding number along the Likert scale. Subjects were first shown an example, then given the scale to complete themselves. The total score was determined by first reverse coding energy-related terms, and then averaging across all 18 items (score range 0–10) with higher scores indicating greater fatigue. Cronbach's alpha was > .90 across all visual analog scale measures before and after cognitive fatigue tasks. The difference between pre- and post-task visual analog scale scores (ΔCF) was used to quantify cognitive state fatigue with high scores indicating more CF experienced from the tasks. Unlike the case of physical fatigue, where perceived and performance fatigability severity can be correlated (Schnelle et al. 2012), objective and subjective reports of cognitive fatigue are often independent of each other (Bailey et al. 2007). Additionally, there are not good cognitive performance-based measures for gambling tasks. We have therefore not calculated "perceived fatigability" scores for the cognitive domain, as was done for the physical domain. ΔCF from executive function tasks was used as the primary CF measure with difference in score before and after gambling tasks (ΔCF_g) recorded as a validation measure. Of note, ΔCF and ΔCF_g were significantly correlated across all subjects (Pearson's $r = 0.65$, $p < 0.0001$). We therefore consider gambling tasks as an independent measure of cognitive fatigue.

Z-scores for the primary fatigue measures, ΔCF and perceived fatigability severity, were calculated and k-means clustering was applied to generate three groups (see Fig. 1a): (1) low CF/low PF, (2) low CF/high PF, and (3) high CF/low PF. Clustering was performed with the K-Means Cluster Analysis procedure implemented in SPSS 25.0.0 (IBM Corporation, Armonk, NY), using a maximum of 10 iterations and requiring zero change between iterations for convergence. This was achieved in 3 iterations for the current data. In the following analyses, the low CF/low PF group was considered a reference, while other groups were compared to this reference.

Image acquisition and analysis

Data were collected using a 3 T Siemens Trio TIM scanner (Siemens Medical Solutions USA, Inc., Malvern, PA) equipped with a 32-channel receive-only head coil transmission. Each session began with a scout image, followed by either a DTI or T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) scan. MPRAGE scans were performed with TR/TE = 2530/3.44 ms, TI = 1100 ms, flip angle = 7°, matrix = 256 × 256, resolution 1x1x1 mm, 192 slices. DTI was performed using a 2D axial single-shot dual-echo SE-EPI sequence with TR/TE = 9000/86 ms, matrix = 128 × 128, field of view = 256 × 256 mm^2, 2 mm slice thickness with no gap (60 slices for whole brain coverage), iPAT (GRAPPA) acceleration factor = 2, number of diffusion-weighted directions = 60 with b = 1000 s/mm^2 and 1 average, and b = 0 images with 10 averages.

DTI data were processed using the population-based structural connectome pipeline (see Fig. 2), which has been described previously (Zhang et al. 2018c). Briefly, this pipeline performs high angular resolution diffusion (HARDI) tractography with anatomical priors, registers this data to parcellated T1 data for the same subject, and groups each tractography dataset into bundles connecting specified regions of interest (see Fig. 2, second panel). This yielded connectome matrices for each subject, where each element represents a particular measure along the connection between two regions of interest (see Fig. 2, third panel). We examined mean and maximum fractional anisotropy (FA_{mean}, FA_{max}) and mean diffusivity (MD_{mean}, MD_{max}), connected surface area, and total number of connections. FA and MD are diffusion-related features representing the anisotropy of diffusion and absolute diffusion, respectively, while number of connections and connected surface area are endpoint-related features indicating the number of streamlines connecting two regions and the area those streamlines intersect, respectively. ROIs were 68 cortical

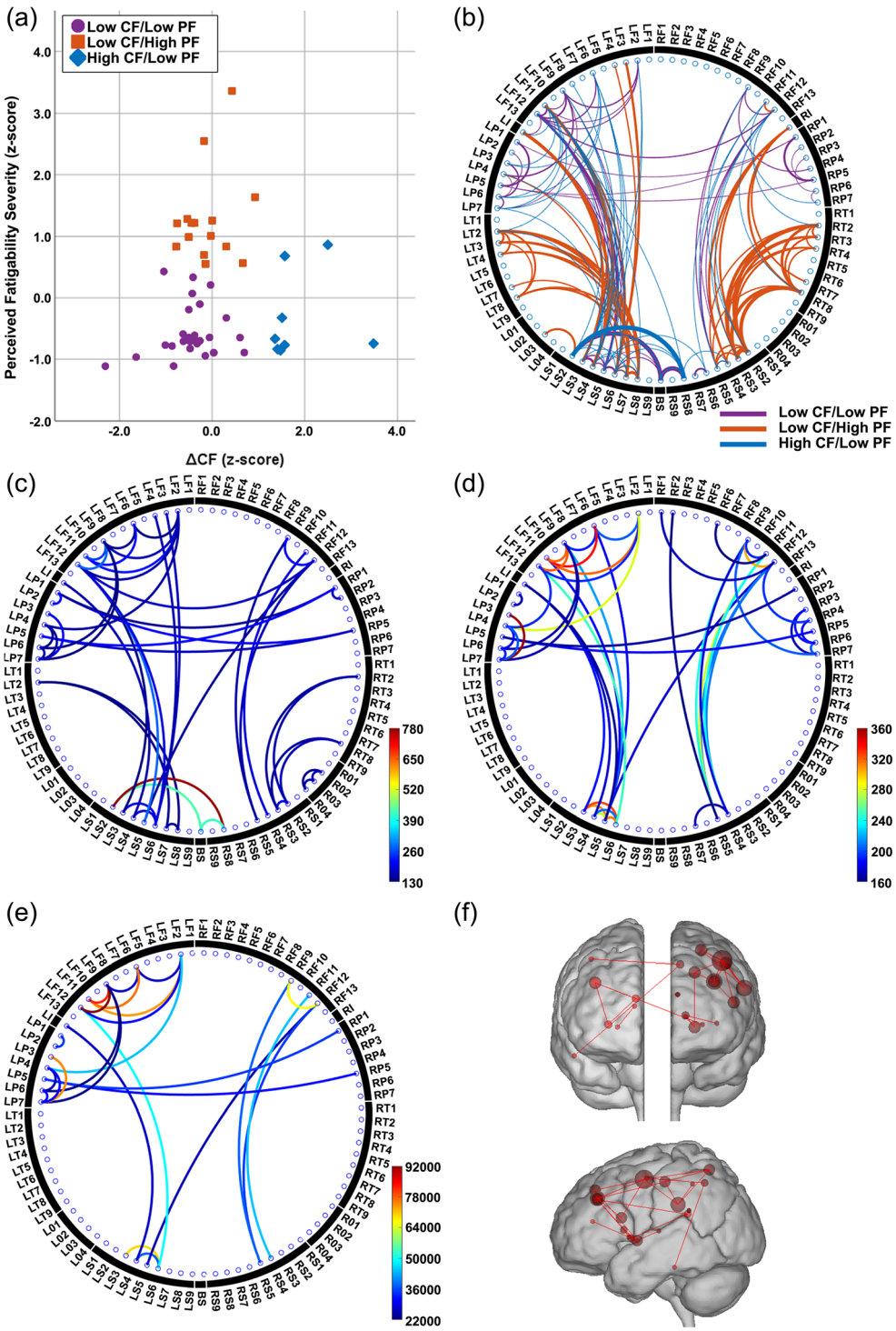

Fig. 1 Tensor network principal component analysis demonstrates differences in connected surface area between high and low fatigue subjects. a ΔCF and perceived fatigability severity z-scores for all subjects, with groups generated based on k-means clustering. **b** Structural connectome maps representing connected surface area in the top 50 connections in principal brain networks for each of the analyzed groups, with line thickness representing relative connected surface area. **c** PC score difference map for the top 50 connections that were most different for the PF comparison. Line color represents mean absolute difference in PC score. **d** PC score difference map for the top 50 connections that were most different for the CF comparison. Line color represents mean absolute difference in PC score. **e** Product of PC scores for connections shared between the PF and CF comparisons. Line color represents product of mean absolute PC score differences for PF and CF comparisons. Individual region labels are provided in Supplemental Table 1. **f** Common structural connections between PF and CF comparisons. Node size indicates the relative number of other regions a particular region is connected to

and 18 subcortical regions from the Desikan-Killiany atlas (Desikan et al. 2006), and brainstem. Parcellation of T1 images was performed with FreeSurfer (v6.0.0, surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki). This pipeline yielded an 87x87x6 tensor per subject, containing all connections between the 87 ROIs for all 6 DTI metrics analyzed.

Tensor network principal component analysis

In order to analyze high-dimensional connectome data (we have 22,446 variables if we vectorize the six connectivity matrices), we performed tensor network principal component analysis (TN-PCA) (Zhang et al. 2018b).

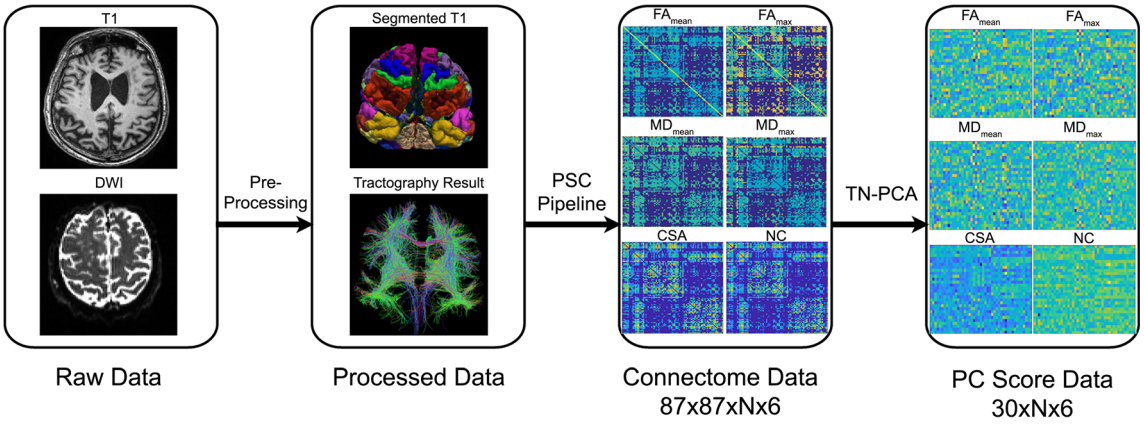

Fig. 2 DTI data processing. Processing pipeline for DTI data, illustrating pre-processing, population-based structural connectome (PSC) pipeline, connectome matrices, and TN-PCA. Individual results are shown for a representative case from the low CF, high PF group

This technique uses a semi-symmetric tensor generalization of PCA to represent the full connectome using K principal components, each of which represents a simplified tensor network consisting of a subset of the full connectome. This is represented mathematically as

$$X = \sum_{k=1}^{K} d_k * U_k(i,k) * v_k \circ v_k, \quad (1)$$

where X is the 87x87xN tensor representing a particular connectome for all subjects, d_k is a scaling factor, $v_k \circ v_k$ represent the basis networks, and $U_k(i,k)$ are a set of vectors $[u_1,\ldots,u_k]$, where each represents a set of principal component coefficients for a particular subject. 30 principal components were used in order to avoid overfitting and sufficiently explain the variation in the data, while preserving model simplicity.

TN-PCA was performed for all subjects, for each of the 6 metrics, using 30 principal components. Thus, each 87x87xN connectome was represented in reduced dimensionality as a 30xN matrix containing 30 PC scores per subject (see Fig. 2, fourth panel). Maximum mean discrepancy (MMD) testing (Gretton et al. 2012) was used to perform pairwise comparison of PC scores between the low CF/low PF group and the low CF/high PF (PF comparison) or high CF/low PF (CF comparison) group in order to select features for validation and prediction of fatigue. Correction for multiple comparisons was not performed on the results of MMD testing, as the goal was to identify candidate DTI metrics for prediction of fatigue.

Reconstruction of principal brain networks

As shown in Eq. (1), TN-PCA results in a set of basis networks that are weighted by a scaling factor d_k and a set of subject specific coefficients U_k. If we take the mean U_k across a group of subjects, we can construct the average brain basis network for each principal component. Summing across principal components results in a representative weighted brain network for a group of subjects that we call the principal brain network (Zhang et al. 2018b). By thresholding these principal brain networks, we can generate sparse structural connectivity maps that illustrate the connections that best explain the full brain connectome. Group principal brain networks were generated using absolute mean differences between the U_k for individual groups. A PF comparison principal brain network was generated by weighting the reconstruction described above by $|U_{k,low\ CF/low\ PF} - U_{k,low\ CF/high\ PF}|$ and a similar CF comparison network was created using $|U_{k,low\ CF/low\ PF} - U_{k,high\ CF/low\ PF}|$. Overlapping connections were identified by multiplying the PF comparison principal brain network by the CF comparison principal brain network. These principal brain networks can be utilized to examine group differences in structural connectomes. To do this, independent principal brain networks were generated for the CF and PF comparisons, and the 50 connections with the largest weight were considered for display and analysis.

Prediction of fatigue

Correlation between top connected surface area connections and measures of cognitive or physical fatigue was computed using simple linear partial correlation coefficients, with age, gender, and education as covariates.

For internal validation purposes, PC scores were used to predict group membership. We performed 5-fold cross-validated logistic regression, using age, gender, education, and PC scores for each subject as predictors. Groups were compared on a pairwise basis.

If a shared neural circuit underlying resilience to fatigue from two fatigue manipulation tasks (ΔCF and perceived fatigability severity) exists, this circuit should also be linked to any perceived fatigue such as CF generated from gambling tasks (ΔCF_g) or PF based on a retrospective evaluation of fatigue-manipulation tasks experienced in the last month (Pittsburgh fatigability score). We therefore examined prediction of fatigue by connected surface area in the overlapping regions between the CF and PF comparison principal brain

networks using support vector machine regression. Epsilon insensitive linear support vector machine regression was performed to predict subjective fatigue measures based on the top 50 connections identified with TN-PCA for the overlapping connections shown in Fig. 1e, with age, gender, and education as covariates. This was performed independently for ΔCF_g and the Pittsburgh fatigability score, as these measures were not used to generate the examined groups. A linear kernel was used with the kernel scale factor, box constraint, and ε optimized automatically, sequential minimal optimization, and 5-fold cross-validation (fitrsvm, MATLAB 2017a, The MathWorks, Inc., Natick, MA). This prediction was additionally performed without structural connectome information (covariates-only). The improvement in prediction of fatigue by the addition of structural connectome information was quantified by

$$PI = \frac{R^2_{full} - R^2_{cov\_only}}{R^2_{cov\_only}} * 100, \quad (2)$$

where PI is the percentage improvement in prediction, $R^2_{cov\_only}$ is the coefficient of determination for the covariates-only regression model and R^2_{full} is the coefficient of determination for the model incorporating both covariates and connectome information.

Statistical analysis

Continuous variables were compared using one-way ANOVA, with post-hoc testing using Tukey's test. Gender data were compared using Chi-square test. TN-PCA and regression analyses were performed in MATLAB (The MathWorks, Inc., Natick, MA). All other analyses were performed with SPSS (v25, IBM Corporation, Armonk, NY).

Results

Participant characteristics

Demographics (age, gender, education) were similar between groups, with multiple self-reported measures of cognitive and physical fatigue showing the expected group differences (see Table 1).

Tensor network principal component analysis demonstrates differences in connected surface area between high and low fatigue subjects

DTI data processing yielded multiple structural connectome matrices for each subject. Of the 6 metrics examined, only connected surface area showed significant group differences (under the significance level $\alpha = 0.05$) in PC scores when comparing the two groups (high CF/low PF or high PF/low CF) with the reference (low CF/low PF, see Table 2). We therefore focus our subsequent analysis on connectomes involving the connected surface area feature.

Principal brain networks reveal group differences in bi-hemispheric connectivity

The results of TN-PCA can additionally be used to reconstruct principal brain networks, which represent the weighted brain network for a group of subjects. These principal brain networks are shown for each of the three groups in Fig. 1b for the case of connected surface area. Here, we have chosen to display the top 50 connections of the 3741 possible combinations possible for the selected set of ROIs, with thicker lines indicating greater connection strength. As can be seen, all 3 groups show strong subcortical connections. The group with low fatigue (low CF, low PF) has connections across hemispheres, while the other two groups, with either high CF or PF, have only within-hemisphere connections.

Differences in principal brain networks between cognitive and physical fatigue

These principal brain networks can additionally be utilized to examine group differences in structural connectomes. Mean absolute differences in PC scores are shown in Fig. 1, for the case of low CF/low PF vs. low CF/high PF (PF comparison, Fig. 1c) and low CF/low PF vs. high CF/low PF (CF comparison, Fig. 1d). For the PF comparison, we see greater bilateral involvement, with strong connections between left and right superior frontal, left and right cerebellum cortex, and left putamen and right superior frontal. For the CF comparison, we see greater interconnection of the frontal and parietal regions, with few connections between hemispheres.

Principal brain networks reveal shared neural circuitry for resilience to physical and cognitive fatigue

Since there was no group with both high CF and PF, the union of the CF and PF comparison principal brain networks was used to evaluate connections shared between the two fatigue comparisons. This product of the PF comparison and CF comparison principal brain networks is shown in Fig. 1e. As can be seen, there are 26 connections in common between the CF and PF comparisons (shown in Fig. 1f, and listed in Table 3), particularly between frontal, parietal, and striatal regions within each hemisphere. This may indicate structural connections that are important for the processes of both cognitive and physical fatigue. Of particular note is the lack of bilateral connections, with only the right thalamus and left superior frontal showing strong connection. The strongest connections shared by CF and PF are all in the left hemisphere, and connect precentral–

Table 1 Group differences in demographics and subjective fatigue measures

	Low CF, Low PF ($n = 29$)	Low CF, High PF ($n = 15$)	High CF, Low PF ($n = 8$)	F/χ^2 (P value)
Age (years)	70.1 ± 4.77	72.9 ± 5.87	69.5 ± 4.38	1.77 ($p = 0.18$)
Gender (% male)	35.7% (18.6–55.9%)	13.3% (1.66–40.5%)	25.0% (3.19–65.1%)	2.49† ($p = 0.29$)
Education (years)	16.5 ± 2.80	17.1 ± 1.94	16.0 ± 2.39	0.51 ($p = 0.60$)
ΔCF	0.080 ± 1.089	0.74 ± 0.93	4.38 ± 1.39*	48.5 ($p < 0.0001$)
ΔCF_g	0.28 ± 1.49	0.67 ± 1.22	2.29 ± 1.60*	6.18 ($p = 0.004$)
Perceived Fatigability Severity	$1.28 \times 10^{-3} \pm 7.35 \times 10^{-4}$	$4.62 \times 10^{-3} \pm 1.37 \times 10^{-3}$*	$1.72 \times 10^{-3} \pm 1.27 \times 10^{-3}$	53.0 ($p < 0.0001$)
Pittsburgh Fatigability Score	11.3 ± 7.39	19.2 ± 7.66*	12.0 ± 8.90	5.39 ($p = 0.008$)

Values are given as mean ± standard deviation, with p values representing results of one-way ANOVA. Gender data are given as % male (95% confidence interval), with p values representing results of Chi-square test. Post-hoc testing was performed using Tukey's test, with the low PF/low CF group as reference. Entries marked with * were significantly different ($p < 0.05$) from the reference group. † χ^2 value

superior frontal, rostral middle frontal–precentral, rostral middle frontal–pars opercularis, supramarginal–inferior parietal, and rostral middle frontal–caudal middle frontal. Of note, these overlapping connections were negatively correlated with ΔCF and perceived fatigability severity (see Table 3); indicating that greater connected surface area was affiliated with lower fatigue for both CF and PF.

Connected surface area in connections shared between physical and cognitive fatigue predict subjective ratings of fatigue

For internal validation purposes, PC scores were used to predict group membership. The group difference between high PF/low CF vs. low PF/low CF was predicted with 63.2% accuracy (area under curve (AUC) = 0.66). The group difference between low PF/high CF vs. low PF/low CF was predicted with 73.3% accuracy (AUC = 0.65).

We next examined prediction of subjective measures of fatigue using a sub-network consisting of the overlapping connections identified using principal brain networks. Here we examined the measures not used for determining fatigue group (ΔCF_g and Pittsburgh fatigability score). Linear support vector machine regression was performed to predict subjective fatigue measures based on the 26 overlapping connections shown in Fig. 1e, with age, gender, and education as covariates. This was additionally performed without structural connectome information (confounders-only), with R^2 values returned by linear support vector machine regression shown in Fig. 3. For these overlapping connections, which may be indicative of the shared fatigue circuitry, Pittsburgh fatigability score was predicted at $R^2 = 0.70$, $p < 0.0001$, and ΔCF_g was predicted at $R^2 = 0.54$, $p < 0.0001$. Inclusion of connectome information in the model improved R^2 by 1.12×10^3% for Pittsburgh fatigability score and 1.23×10^3% for ΔCF_g, indicating that incorporation of connectome information into regression models had a drastic improvement on prediction of subjective fatigue reports compared to covariates-only and that the structural connectome plays an important role in both CF and PF.

Discussion

We monitored fatigue in response to cognitively and physically demanding tasks in healthy older adults. Using a sophisticated connectome extraction pipeline and dimension reduction method, we examined data from diffusion tensor imaging. We found that: 1) there exist structural connectomes of state fatigue across cognitive and physical types, particularly involving connected surface area between frontal, parietal, and striatal regions within each hemisphere. 2) these shared

Table 2 Results of pairwise group PC score comparisons

DTI metric	PF comparison (i.e., high PF/low CF vs. low PF/low CF)	CF comparison (i.e., low PF/ high CF vs. low PF/low CF)
FA_{mean}	0.19	0.068
FA_{max}	0.42	0.29
MD_{mean}	0.64	0.21
MD_{max}	0.14	0.30
Connected surface area	0.046	0.036
Number of connections	0.040	0.20

P values resulting from MMD test for pairwise group comparisons of PC scores for each quantified DTI metric

Table 3 Overlapping connections between CF and PF comparisons

Region 1	Region 2	ΔCF correlation	Perceived fatigability severity correlation
L Precentral	L Superior Frontal	−0.26	−0.11
L Rostral Middle Frontal	L Precentral	−0.01	0.02
L Rostral Middle Frontal	L Pars Opercularis	−0.10	−0.12
L Supramarginal	L Inferior Parietal	−0.25	−0.22
L Rostral Middle Frontal	L Caudal Middle Frontal	−0.27	−0.06
L Pallidum	L Thalamus Proper	−0.02	−0.33*
R Superior Frontal	R Precentral	−0.24	−0.10
L Superior Frontal	L Pallidum	−0.27	−0.18
L Postcentral	L Caudal Middle Frontal	0.00	−0.15
R Rostral Middle Frontal	R Pallidum	−0.04	−0.15
R Precentral	R Putamen	−0.28	−0.21
L Pallidum	L Caudate	−0.26	−0.36*
R Superior Frontal	R Putamen	−0.23	−0.06
L Precuneus	R Isthmus Cingulate	−0.05	−0.19
L Posterior Cingulate	L Isthmus Cingulate	−0.06	0.05
L Superior Parietal	L Supramarginal	−0.39*	−0.29
L Precuneus	R Precuneus	−0.05	−0.21
L Supramarginal	L Postcentral	−0.30	−0.35*
L Superior Frontal	L Caudal Middle Frontal	−0.20	−0.09
L Caudal Middle Frontal	L Pars Opercularis	0.03	−0.22
L Caudate	L Insula	−0.09	−0.24
L Precentral	L Pars Opercularis	−0.22	−0.26
R Superior Frontal	L Putamen	−0.16	−0.16
L Postcentral	L Superior Parietal	−0.09	−0.22
L Superior Parietal	L Precentral	−0.35*	−0.01
L Precentral	L Supramarginal	−0.35*	−0.11

Connections are ranked descending in terms of largest PC score product between comparisons. Correlations between connected surface area in these connections and ΔCF or perceived fatigability severity are given as simple linear partial correlation coefficients, controlled for age, gender, and education. * Significant ($p < 0.05$) correlation

connectomes were negatively correlated with ΔCF and perceived fatigability severity, indicating that greater connected surface area was affiliated with lower cognitive and physical fatigue; 3) these overlapping connections can accurately predict external reports of cognitive (ΔCF_g) and physical (Pittsburgh fatigability score) fatigue. These results suggest robust structural connectomes resilient to the experience of both cognitive and physical fatigue.

As summarized recently (Goni et al. 2018), neural correlates of fatigue in DTI studies of chronic conditions have been varied. Greater FA of the superior frontal gyrus and ACC were linked to fatigue in fibromyalgia (Lutz et al. 2008). The thalamus-frontal tract was linked to cognitive or general fatigue in MS (Bester et al. 2013; Genova et al. 2013), while other studies identified the importance of the right temporal cortex (Bernitsas et al. 2017; Yarraguntla et al. 2018). In traumatic brain injury, the thalamus-frontal tract was linked to cognitive fatigue (Clark et al. 2017). This variability may be primarily explained by the confounding influence of trait fatigue due the disease state on perceived fatigue. Examining state fatigue may help better identify true neural correlates; our study represents the first to reveal the neural substrates underlying state fatigue in healthy individuals.

Previous studies have focused on selective tracts and limited tract characteristics (Bester et al. 2013; Rayhan et al. 2013). We examined MD, FA, connected surface area, and number of connections along all combinations of 87 cortical, subcortical, and brainstem regions. Number of connections and connected surface area are endpoint-related features indicating the number of streamlines between two regions and the area these streamlines intersect. Connected surface area can be interpreted as the robustness of surface connection between two ROIs, and could be a metric for the sensitivity of the connection to neurodegeneration, either disease-related or due to normal aging. We found that connected surface area was significantly different between high and low fatigue

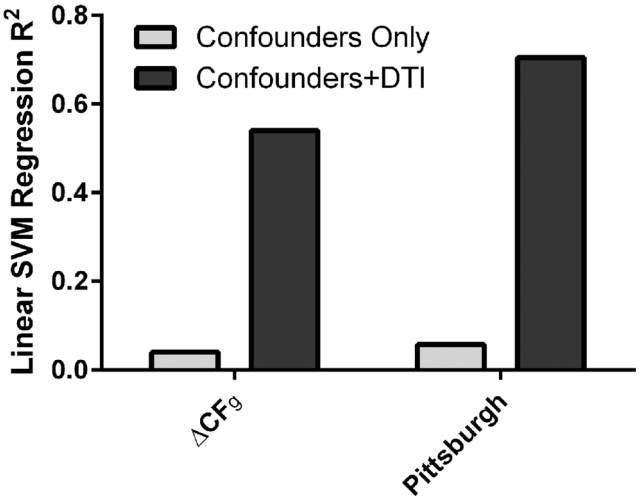

Fig. 3 Connected surface area in connections shared between physical and cognitive fatigue predict subjective ratings of fatigue. Coefficients of determination for linear support vector machine (SVM) regression models relating connected surface area in the overlapping connections between PF and CF comparisons to cognitive and physical fatigue metrics. "Confounders only" models were trained using only age, gender, and education as predictors, while "Confounders+DTI" models were trained using age, gender, education, and the connected surface area in the overlapping connections in the principal brain network as predictors

subjects for both CF and PF, whereas other measures were not. This indicates that the breadth of connection of streamlines in particular brain regions may be more important than the anisotropy or diffusivity along these streamlines. We have previously shown that endpoint-related features, particularly connected surface area, are more robust and reproducible across scans of the same subject, compared to diffusion-related features (Zhang et al. 2018c).

The most prominent tracts identified are within the left frontal, parietal, and basal ganglia regions. Previous fMRI studies have implicated these regions in relation to fatigue in subjects with chronic fatigue syndrome (Cook et al. 2007; Miller et al. 2014), traumatic brain injury (Kohl et al. 2009), and multiple sclerosis (Finke et al. 2015). It is often assumed that functional connectivity is dependent on underlying anatomical and structural connections (Monje 2018), given the critical role white matter tracts have been suggested to play in supporting and shaping brain function (Monje 2018). Evidence indicates that decreases in white matter integrity in old age are related to reduced functional efficiency (Zhu et al. 2015); the current study indicates state fatigue is also related to these white matter decreases. Of note, the primary tracts identified here are superficial white matter tracts (Phillips et al. 2013). Emerging studies emphasize the vulnerability of superficial white matter during aging (Nazeri et al. 2015; Phillips et al. 2013), which may be due to demyelination and/or the number, coherence, or integrity of axons (Fjell et al. 2008). Age-related cognitive deficits associated with superficial white matter changes are often in the right hemisphere (Nazeri et al. 2015), while psychiatric disorders are often associated with superficial white matter deficits in the left or both hemispheres (Zhang et al. 2018a). When examining tracts within CF or PF alone (especially PF), both hemispheres are involved. These findings suggest the importance of understanding fatigue in old age. When considering the interrelationships between fatigue and multiple metabolic processes (Lin et al. 2016; Lin et al. 2013), the occurrence of CF and/or PF may indicate underlying bilateral neural deficits, and be a marker for biological aging.

The current study was performed in a relatively small population, and relied on subjective reports of fatigue. While these reports are well validated (Borg 1982; Glynn et al. 2015; Lee et al. 1991), there is still uncertainty involved. There is some subjectivity in the number of principal components utilized in TN-PCA. 30 principal components were used to sufficiently explain variation in the data, while avoiding overfitting. In a larger study, a greater number of principal components could be used to better explain variation. Group separation was based on k-means clustering of ΔCF and perceived fatigability severity scores. For another population, this could result in different grouping of subjects, which would modify the results yielded. Additionally, as subjects with chronic fatigue were excluded from this study, the results here may not directly implicate chronic fatigue. Further validation of the obtained neural profile is required in a clinically relevant patient population. Finally, although individuals with known neurologic or vascular disorders were excluded, the effects of leukoaraiosis and other markers of cerebrovascular disease were not explicitly controlled for in the analysis. Differences in leukoaraiosis were previously shown between high and low fatigue healthy older adults (Benzi M Kluger et al. 2019), which could influence the results of DTI analysis.

In summary, we have demonstrated the presence of a shared neural circuit involved in resilience to the experience of cognitive and physical fatigue. This circuit involves short white matter tracts located primarily within the left frontal, parietal, and basal ganglia regions. Connected surface area for these tracts is predictive of external fatigue measures that were not used in the generation of the analyzed groups, indicating that the strength of these tracts are a robust predictor of resilience to fatigue. This emphasizes the importance of physical measures of structural connectivity, rather than only those based on diffusion parameters. Further study is warranted to examine the interaction between functional and structural connectivity in the mediation of fatigue.

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Data availability Software used for DTI processing is freely available on GitHub (https://github.com/zhengwu/PSC_Pipeline). The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards The study and all procedures were approved by the local Institutional Review Board. All participants provided written consent.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (University of Rochester Research Subjects Review Board) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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