



Electroencephalography-Derived Functional Connectivity in Sensorimotor Networks in Post Stroke Fatigue

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Abstract

Background Poor suppression of anticipated sensory information from muscle contractions is thought to underlie high fatigue. Such diminished task-related sensory attenuation is reflected in resting state connectivity. Here we test the hypothesis ‘altered electroencephalography (EEG)-derived functional connectivity in somatosensory network in the beta band, is a signature of fatigue in post-stroke fatigue’.

Methods In non-depressed, minimally impaired stroke survivors (n=29), with median disease duration of 5 years, resting state neuronal activity was measured using 64-channel EEG. Graph theory-based network analysis measure of functional connectivity via small-world index (SW) was calculated focusing on right and left motor (Brodmann areas 4, 6, 8, 9, 24 and 32) and sensory (Brodmann areas 1, 2, 3, 5, 7, 40 and 43) networks, in the beta (13–30 Hz) frequency range. Fatigue was measured using Fatigue Severity Scale - FSS (Stroke), with scores of > 4, defined as high fatigue.

Results Results confirmed the working hypothesis, with high fatigue stroke survivors showing higher small-worldness in the somatosensory networks when compared to low fatigue.

Conclusion High levels of small-worldness in somatosensory networks indicates altered processing of somesthetic input. Such altered processing would explain high effort perception within the sensory attenuation model of fatigue.

Keywords Fatigue · Stroke · Electroencephalography · Small word index · Beta band · Connectivity · Sensory network

Introduction

Stroke, a result of vascular insufficiency to neurons present with fatigue as a significant symptom. The severity of stroke does not explain reported levels of fatigue (Kutlubaev et al. 2012; van der Werf et al. 1998). Previously, we have proposed a sensory attenuation hypothesis of fatigue, based on poor suppression of anticipated sensory information – (Kuppuswamy 2017, 2022). Poor suppression of muscle sensory afferents results in assigning high effort to simple tasks which explains a significant proportion of post-stroke fatigue (Doncker et al. 2020a, b) In visual and auditory perception, poor distractor suppression explains post-stroke

fatigue (Kuppuswamy et al. 2022; Doncker and Kuppuswamy 2022). While other brain regions/networks have been implicated in fatigue such as parietal, pre-frontal and sub-cortical networks (Jaeger et al. 2019; Finke et al. 2015; Cotter et al. 2021), here we specifically focus on somatosensory and motor networks which have been implicated in PSF; to test the predictions of the sensory attenuation hypothesis that a dysfunction within the somatosensory networks underlies fatigue.

From a neuronal network functioning point of view, behaviour mirrors structural and functional changes in networks, which persist in resting state (Graziadio et al. 2010). Neuronal networks at rest express features that keep trace of their ability to perform the required behaviour (Kim and Kang 2018; Wahlheim et al. 2022; Doucet et al. 2012; Y. Li et al. 2022a, b; Liu et al. 2022). These features of networks at rest display alterations that reflect chronic symptoms (Porcaro et al. 2019). Both in post-stroke fatigue (PSF) and other disease where fatigue is significant, neurophysiological (Kuppuswamy et al. 2015a, b, c; Ondobaka et al. 2021; De Doncker et al. 2021; Liepert et al. 2005; Morgante et al.

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2011; Russo et al. 2017) and behavioural (Kuppuswamy et al. 2015a, b, c, 2016; De Doncker et al. 2020a; Doncker et al. 2020b) findings support an altered resting state, specifically sensory network activity.

Ensembles of neurons that fire at specific frequencies and communicate with each other by synchronising their firing, comprise a neuronal network. To understand a network's activity, the strength of synchronicity between various nodes is mapped using functional connectivity methods (Bullmore and Sporns 2009). Functional connectivity is defined as the temporal correlation or dependency between distinct neuronal groups and areas (Fingelkurts et al. 2005; Rubinov and Sporns 2010). Such temporal correlation occurs in various frequency bands, with low frequencies associated with arousal, mid-range frequencies related to sensorimotor activity, and high frequencies representing higher order functions such as error detection and learning. With PSF proposed to be a problem of sensorimotor control, specifically arising from processing of incoming muscle related sensory information, we anticipated a fatigue related modulation of beta band frequency.

Here we investigate if a dysfunction of somatosensory networks underlies PSF, as demonstrated by changes in

beta-band neuronal activity in sensory and motor networks at rest.

Methods

Participants

This study was approved by the London Bromley Research Ethics Committee (REC reference number: 16/LO/0714). Stroke survivors were recruited and tested at the Institute of Neurology, London, UK.

All stroke survivors were screened prior to the study based on the following criteria: first-time ischaemic or haemorrhagic stroke; stroke occurred at least 3 months prior to the study; no clinical diagnosis of any other neurological disorder; physically well recovered following their stroke defined as grip strength and manual dexterity of the affected hand being at least 60% of the unaffected hand assessed using a hand-held dynamometer and the nine-hole peg test (NHPT) respectively; not taking anti-depressants or any other medication that has a direct effect on the central nervous system; not clinically depressed with depression scores ≤ 11 assessed using the Hospital Anxiety and Depression Scale (HADS)(Snaith 2003).

Twenty-nine stroke survivors took part in the study (Table 1) and provided written informed consent in accordance with the Declaration of Helsinki. A formal sample-size calculation was not performed due to lack of pilot data. However, in previous studies, differences could be observed in the measure of resting state functional connectivity in as few as 10 subjects per group (Nordin et al. 2016).

Fatigue

Trait fatigue was quantified using Fatigue Severity Scale, FSS-7. An average score of one indicates no fatigue while an average score of seven indicates maximum fatigue (Krupp et al. 1989). High fatigue was defined as FSS-7 > 4 (Valko et al. 2008).

Control group: Healthy humans were not recruited for this study as a control group, specifically as the state of the brain is likely to have changed after an injury or establishment of a disease (Kuppuswamy 2023), therefore an ideal control group will be a within-disease control group. The stroke low (no) fatigue group was used as a control for this study.

EEG Recording

Whole-scalp electroencephalography (EEG) data was recorded using 64-channel systems, ActiCap, Herrsching,

Table 1 This table provides the demographic and lesion information of the stroke survivors cohort

Variable	Fatigue Group	
	Low Fatigue, N = 16 ¹	High Fatigue, N = 13 ¹
FSS-7	2.1 (1.4,2.4)	5.6 (5.3,6.0)
Age (years)	61.7 (55.6,64.8)	62.9 (56.1,68.1)
Sex		
Male	13	5
Female	3	8
Grip Strength (% unaffected hand)	98.4 (89.9,107.3)	92.3 (79.7,103.3)
NHPT (% unaffected hand)	94.3 (86.0,105.)	87.7 (69.4,94.8)
SDMT	1.0 (0.8,1.2)	0.8 (0.5,1.0)
HADS - Anxiety	4.0 (2.8,7.3)	9.0 (3.0,10.0)
HADS - Depression	4.0 (3.0,5.0)	7.0 (3.0,9.0)
Hemisphere Affected		
Left	10	6
Right	6	7
Type of Stroke		
Ischaemic	14	12
Hemorrhagic	2	1
Vascular Territory Affected		
MCA	8	8
PCA	1	1
Brainstem/Cerebellum	3	3
Time Post-Stroke (years)	5.3 (4.2,6.8)	7.4 (5.4,11.1)

¹Median (25%,75%); n

Germany, and a BrainAmp, at rest, with eyes open and focusing on a fixation cross. Duration of recording was seven minutes. The 64 electrodes were positioned on the cap in accordance with the 10–20 international EEG electrode array. During online recordings, channels FCz and AFz were used as reference and ground respectively. Impedances were kept below 10 k Ω throughout the recording. The EEG signal was sampled at 1 kHz and visualized online using the BrainVision Recorder Software (BrainVision Recorder, Version 1.21.0102 Brain Products GmbH, Gilching, Germany).

EEG Analysis

EEG analyses were performed with a combination of EEGLAB (Delorme and Makeig 2004) and custom Matlab scripts. EEG data was down-sampled to 250 Hz and then band-pass filtered from 0.1 to 47 Hz using a finite impulse response filter. Noisy channels were identified and removed using automated procedures. EEG data was subsequently segmented into two second epochs, and epochs containing noisy data were identified as follows: the mean activity of all EEG channels was computed, and the threshold was set at ± 2 times the standard deviation of the mean activity. Epochs containing activity exceeding the threshold value were marked and subsequently removed. This left a total of 160 (± 15) two second epochs. To identify and remove ocular movements and blink artifacts from the EEG data, an independent component analysis (ICA) implemented within EEGLAB was used. ICA is a blind source decomposition algorithm that enables the separation of statistically independent sources from multichannel data (Jung et al. 2000). The components were subsequently visually inspected and those containing ocular movements or blink artifacts were removed. The previously removed channels were then interpolated back into the dataset and finally, the EEG data was re-referenced against the grand average of all scalp electrodes.

Graph Theory Estimates

Functional Connectivity Analysis. EEG connectivity analysis was carried out using the exact low-resolution electromagnetic tomography (eLORETA) software (The KEY Institute of Brain-Mind Research University Hospital of Psychiatry, Zurich; <http://www.uzh.ch/keyinst/New-LORETA/LORETA01.htm>). The eLORETA algorithm is a well-established linear inverse solution for EEG signals (Pascual-Marqui 2002).

Following whole brain sources reconstruction, connectivity was computed using the eLORETA software on four brain regions, divided into motor and sensory networks of the left and right hemisphere based on Broadmann areas

(BAs). Each BA is a region of interest (ROI). The BAs that formed the motor network for both the left and right hemisphere included BA4, 6, 8, 9, 24 and 32, while the BAs that formed the sensory network for both the left and right hemisphere included BA1, 2, 3, 5, 7, 40 and 43.

Current density time series of all BAs within each of the four networks was computed in eLORETA and used to estimate the functional connectivity using the Lagged Linear Coherence (LagR) algorithm, not affected by volume conductance and low spatial resolution in each of the four networks (Pascual-Marqui 2007). Lagged Linear Coherence was computed for beta (13–30 Hz) band frequency.

Graph Analysis. A network is a mathematical representation of a real-world complex system and is defined by a collection of nodes (vertices) and links (edges) between pairs of nodes. Nodes in large-scale brain networks represent brain regions, while links represent anatomical or functional connections. Nodes should ideally represent brain regions with coherent patterns of anatomical or functional connections. The connectivity parameters extracted between all pairs of ROIs for each frequency band is in the form of a square matrix W , with dimensions equal to the number of ROIs. Each row and column within matrix W represent nodes, while the values within the matrix represent the strength of connection between each pair of nodes.

Once the networks of interest were constructed, the core measures of graph theory that summarize the aspects of segregation and integration of a network were computed using the Brain Connectivity Toolbox (Rubinov and Sporns 2010). Segregation refers to the degree to which network elements form individual and separate clusters and is measured by the clustering coefficient (C). Integration refers to the capacity of the network to become interconnected and exchange information and is measured by the parameter characteristic path length (L). The clustering coefficient and characteristic path length represent the efficiency of the network with respect to local and global connectedness respectively. Weighted clustering (C_w) coefficient and weighted characteristic path length (L_w) were computed as a measure of segregation and integration of the network as follows:

$$C_w = \frac{C_{\text{brain}}}{C_{\text{random}}} \text{ and } L_w = \frac{L_{\text{brain}}}{L_{\text{random}}}$$

Where C_{brain} and L_{brain} are the clustering coefficient and characteristic path length derived from the connectivity matrix of each participant. C_{random} and L_{random} are the mean values of the clustering coefficient and characteristic path length of 100 surrogate random networks that have the same basic characteristics as the original network that were derived by randomly rewiring the nodes using the original network edge weights. The random networks preserve the

same basic characteristics as the original network such as the number of nodes and edge weights. The random networks were constructed by Brain Connectivity Toolbox²⁹. A measure of network small-worldness (Sw) was therefore defined as the ratio between Cw and Lw ; the ratio between local connectedness and the global integration of the network.

$$Sw = \frac{Cw}{Lw}$$

When Sw has a value of approximately 1, a network is said to have “small-world properties” meaning a good combination of high levels of local clustering among nodes and proper paths that globally link all network nodes (all nodes of a large system are linked through relatively few intermediate steps). Sw values greater than 1 suggest high levels of local clustering among nodes and many short paths that globally link all nodes of the network, while Sw values less than 1 suggest poor local connectivity and stunted connections.

Statistical Analysis

All statistical analysis was performed using R (RStudio Version 1.2.5033). Spearman rank correlations identified associations between trait fatigue (FSS-7) and demographic variables (age, grip strength, NHPT, HADS – Depression, HADS – Anxiety and Time Post-Stroke). Wilcoxon rank sum tests identified association between trait fatigue (FSS-7 scores) and categorical measures (sex, hemisphere affected and type of stroke). The effect of vascular territory on FSS was not analysed as there were too few in each group. Shapiro-Wilk’s test of normality assessed distribution of dependent variable and Levene’s test assessed homogeneity of variances.

In normally distributed variables, a three-way mixed ANOVA was performed to evaluate the effects of fatigue (between subject factor: $Stroke_{Low}$, $Stroke_{High}$) and sex (between subject factor: Male, Female) on small worldness within the beta frequency band (dependent variable), for two networks (sensory and motor) and two hemispheres (left and right). Greenhouse-Geisser epsilon adjustment corrected any deviations from sphericity. Post-hoc pairwise comparisons (t-tests) with Bonferroni adjustment was performed to identify main effects.

Results

Participant Demographics

Twenty-nine stroke survivors completed the study (11 females and 18 males). The median FSS-7 score was 5.29 (IQR = 2.57) in females and 2.50 (IQR = 2.46) in males. The Wilcoxon test showed that the difference in FSS-7 score was marginally non-significant ($p = 0.05$, effect size = 0.37). Spearman rank correlations between trait fatigue (FSS-7) and all continuous demographic measures revealed a significant positive association between trait fatigue and HADS-Depression (Spearman $\rho = 0.41$, $p = 0.03$), while no other variable correlated with trait fatigue (Age: Spearman $\rho = 0.02$, $p = 0.91$; Grip strength: Spearman $\rho = -0.23$, $p = 0.24$; NHPT: Spearman $\rho = -0.25$, $p = 0.19$; HADS-Anxiety: Spearman $\rho = 0.35$, $p = 0.06$).

Clinical Characteristics

There were no confirmed MRI lesions in any of the stroke survivors in the study. The association between trait fatigue (FSS-7) and the clinical characteristics of the stroke was assessed across all stroke survivors. The median FSS-7 score in those with right hemisphere strokes was 4.43 (IQR = 3.00) and 2.71 (IQR = 3.75) in those with left hemisphere strokes (Wilcoxon test: $p = 0.50$, effect size $r = 0.13$). The median FSS-7 score in those with ischemic strokes was 2.93 (IQR = 3.46) and 3.86 (IQR = 2.29) in those with hemorrhagic strokes (Wilcoxon test: $p = 0.51$, effect size $r = 0.13$). Regarding the vascular territory affected, the data from five stroke survivors was missing as the clinical notes could not be retrieved. The median FSS-7 score in those where the MCA was affected was 3.36 (IQR = 3.25), the median FSS-7 score in those where the PCA was affected was 3.07 (IQR = 2.07), while the median FSS-7 score in those where the Brainstem/Cerebellum was affected was 4.21 (IQR = 2.68) (Kruskal-Wallis test: $p = 0.57$, effect size $\eta^2 = -0.04$). A spearman rank correlation between FSS-7 and the Time Post-Stroke at which the participants took part in the study showed no significant association (spearman $\rho = 0.08$, $p = 0.67$). Any meaningful interpretation of the effect of the type of stroke and vascular territory affected on FSS-7 in the current cohort of stroke survivors is difficult given the skewed numbers.

Small Worldness

Across the two networks (sensory/motor) and hemispheres (left/right) there were two extreme outliers (both in the motor network of the right hemisphere). After exclusion of outliers, the data was normally distributed,

($p > 0.05$) and variances were homogenous ($p > 0.05$). The three-way-ANOVA revealed a main effect of network type ($F_{(1,23)} = 15.59$, $p < 0.01$, $\eta^2 = 0.13$) and a significant interaction between network type and fatigue level ($F_{(1,23)} = 16.79$, $p < 0.01$, $\eta^2 = 0.14$) on small worldness in beta frequency band. There was also a significant three way interaction between network type, fatigue level and sex ($F_{(1,23)} = 5.09$, $p = 0.03$, $\eta^2 = 0.05$), however there was no significant two way interaction between sex and network type ($F_{(1,23)} = 0.65$, $p = 0.43$, $\eta^2 = 0.006$) nor between sex and fatigue ($F_{(1,23)} = 1.05$, $p = 0.32$, $\eta^2 = 0.009$). Post-hoc multiple pairwise comparisons revealed a significant difference in small worldness within the beta frequency band (Fig. 1) between the Stroke_{Low} and Stroke_{High} groups in the sensory network of the right hemisphere ($p = 0.01$), driven by the difference in female participants ($P = 0.0127$). There was also a significant difference between Stroke_{Low} and Stroke_{High} in left and right motor networks ($p = 0.02$ and $p = 0.03$ respectively), with females driving the difference in the right hemisphere ($P = 0.0138$).

Discussion

In twenty-nine patients with stroke, we show that those with high levels of trait fatigue exhibited significantly higher levels of small worldness in the sensory networks and significantly lower levels of small worldness in the motor networks in the beta band frequency (13–30 Hz). There was no association between clinical features of stroke, and trait fatigue which confirms previous findings (Kutlubaev et al. 2012). As investigated by small worldness, functional brain connectivity simultaneously reconciles the opposing demands of functional integration and segregation. The small-world index reflects the balance of functionally specialized (segregated) modules with a robust number of intermodular (integrating) links. Here we observed that fatigue is paralleled by the alteration of small-world organization in sensory and motor networks.

The observed changes in sensory networks are lateralised. A possible trivial explanation could be that the small numbers have resulted in one side reaching significance and not the other. If the observed lateralisation is not due to limited numbers, ‘hyper-connectivity’ in right sensory networks is in keeping with recent findings of a shift towards right hemispheric dominance in sensorimotor networks in

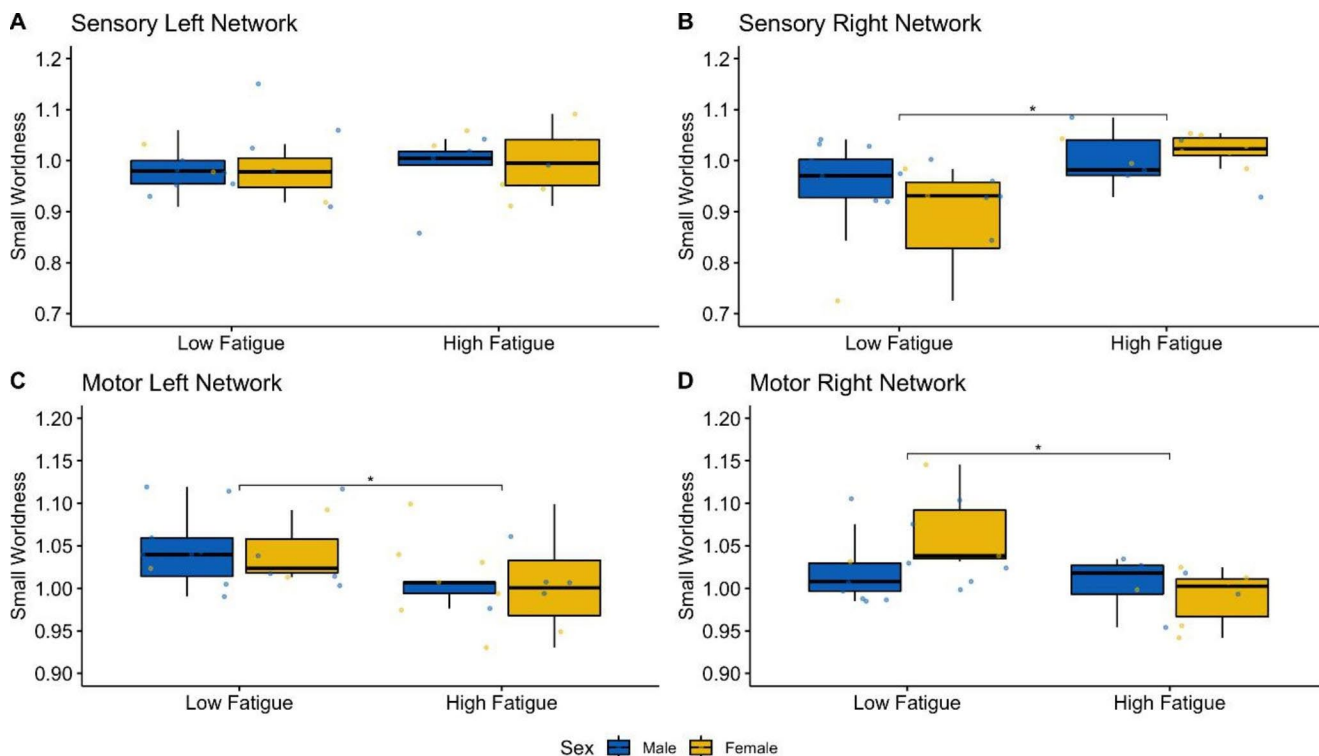


Fig. 1 Functional Connectivity of the Sensory and Motor Networks in the beta band frequency. The value of Small Worldness across the two fatigue groups both in males and females (Stroke_{Male} in blue and Stroke_{Female} in yellow) is displayed using boxplots for the sensory network in the left (A) and right (B) hemispheres and for motor net-

works in the left (C) and right (D) hemispheres. Significant differences between fatigue groups are indicated using asterisks (* = $p < 0.05$). In the right motor and sensory networks, the difference is driven by females

those with high post-stroke fatigue (Ondobaka et al. 2021). Healthy brains exhibit left-hemispheric dominance (Netz et al. 1995; Giovannelli et al. 2009) and a shift towards right dominance has been observed in several psychiatric diseases including depression (Lefaucheur et al. 2008). A third possible non-trivial explanation could be the small difference in the number of left hemispheric strokes in the low fatigue group, however, this is unlikely as previous studies show shift in hemispheric dominance regardless of the side of stroke (Ondobaka et al. 2021).

Beta band activity is commonly known as the sensorimotor ‘idling’ rhythm seen in all cortical and sub-cortical motor areas at rest. Movement desynchronises beta band oscillations which lead to the idea that beta frequency is the rhythm of rest for sensorimotor areas. Recent proposals suggest that beta band activity may not simply reflect a lack of movement but is rather an indicator for maintenance of sensorimotor status quo (Engel and Fries 2010). During periods of spontaneous enhancement in resting beta band activity, movements are slower, than when resting beta activity is lower (Gilbertson et al. 2005). In light of such findings, the current results indicate that those with high fatigue are likely to have slowed movements. In post-stroke fatigue, while there is no difference in reaction times, there is slowing of movements (Kuppuswamy et al. 2015a, b, c), perhaps because there is a resistance to change sensorimotor status quo as reflected by enhanced beta rhythm small-worldness shown in this study.

It is well-established that fatigue is only marginally associated with motor and cognitive deficits (Ingles et al. 1999; Winward et al. 2009). However, despite good functional ability, markers of poor behavioural flexibility is associated with high fatigue (De Doncker et al. 2021; Morgante et al. 2011). Enhanced sensory, and diminished motor network functional connectivity that seeks to maintain a sensory state, thereby making new sensory states less desirable, lends further support to the idea of poor behavioural flexibility underpinning high fatigue.

In this study we provide evidence for alteration in somatosensory processing, which may indicate a possible mechanism that drives fatigue is poor somatosensory processing. Both in post-stroke fatigue and other neurological conditions such as MS, there are several reports of altered resting state connectivity (Ondobaka et al. 2021; Woodward et al. 2019; Bisecco et al. 2018; Jaeger et al. 2019; Stefancin et al. 2019; Cotter et al. 2021). In stroke, suggestions of parietal hypoconnectivity and frontal hyper connectivity (Cotter et al. 2021) with reversed inter-hemispheric balance of connectivity (Ondobaka et al. 2021), are implicated in manifestation of fatigue. In MS, changes in default mode network (Jaeger et al. 2019) and involvement of striatal circuits involved in movement, sensation and motivation

(Bisecco et al. 2018) have all been implicated in development of fatigue. While several brain regions have been implicated in both diseases as the core regions involved in fatigue, very few of the studies performed hypothesis driven analysis on resting state activity. In the present study, we hypothesised that attention to somatosensory input is not suppressed as normal [indicated by high perceived effort during muscle contraction (Doncker et al. 2020a, b)] which will be reflected in the resting state both in sensory and motor networks. Hyper-connectivity in sensory networks, commonly seen as a marker of tendency to maintain sensory states quo, and resultant hypoconnectivity in motor networks that indicate lower M1 excitability (Kuppuswamy et al. 2015a, b, c) supports the premise that poor somatosensory attenuation underpins high PSF. In summary, increased small world-ness in somatosensory networks suggests a propensity to maintain the status quo i.e. rest; an increased propensity to inaction (rest) translates into an increase in the effort needed to initiate an action; increased effort results in fatigue.

The high fatigue group had a disproportionately high number of females when compared to the low fatigue group. Previous studies have reported greater incidence of fatigue in female stroke survivors (Cumming et al. 2016) and sex significantly influences measures of resting state connectivity (Stumme et al. 2020). While difference in incidence of fatigue was previously attributed to factors such as reporting biases influenced by sociocultural factors, the difference in resting state connectivity between males and females with high fatigue seen in this study opens up the possibility of a biological basis for differences in incidence of PSF. The influence of sex on resting state connectivity regardless of fatigue or stroke is unlikely to be the driver of the differences seen here, as sensorimotor networks are less likely to be influenced by sex (L. Li et al. 2022), unlike other brain networks. While further speculation on differences in biological mechanisms driving fatigue in males and females is beyond the scope of this paper, future mechanistic studies in fatigue must consider the possibility of sex being a confounding factor in interpretation of findings, and also directly study differences between males and females in PSF.

Limitations: While the hypothesis-driven approach of this study is a strength, it could also be a limitation. No neural network in the brain operates in isolation and the influences of other networks on sensorimotor areas of the brain are also likely influenced by the differences seen in this study, which needs further investigation. The relatively small numbers of participants in this study is further highlighted by the differences seen between sexes in this study. Lesion location does not influence PSF incidence or severity, however, to definitively exclude influence of lesion location on neural

network activity relevant to fatigue, greater numbers in each lesion type is warranted.

Conclusion

Chronic fatigue is a feature of several established long-term disorders. However, there is no principled framework to understand the mechanisms of fatigue. In this paper, we demonstrate sensorimotor network activity is altered in line with the predictions of the sensory attenuation model of fatigue in chronic stroke survivors. This is a promising framework which could explain altered connectivity seen in other neurological disorders with long-term fatigue and future work must focus on exploring sensory attenuation in chronic fatigue.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10548-023-00975-8>.

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Author Contributions CW performed the functional connectivity analyses, and wrote the manuscript. WD performed data collection in stroke cohort, produced the figures and performed the statistical analyses. AK obtained funding, wrote and revised the manuscript.

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Data Availability The processed EEG data is available on request from a.kuppuswamy@ucl.ac.uk.

Declarations

Competing Interests The authors declare no competing interests.

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