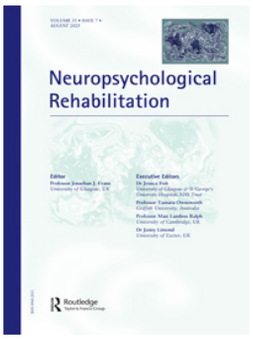

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Post-stroke fatigue severity is associated with executive dysfunction in chronic stroke

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ABSTRACT

Following stroke, fatigue is highly prevalent and managing fatigue is consistently rated a key unmet need by stroke survivors and professionals. Domain-specific cognitive impairments have been associated with greater fatigue severity in earlier stages of stroke recovery, but it is unclear whether these associations hold in chronic (>2 years) stroke. The present cross-sectional observational study evaluates the relationship between domain-specific cognitive functioning and the severity of self-reported fatigue among chronic stroke survivors. Participants (N = 105; mean age = 72.92, 41.90% female; mean years post-stroke = 4.57) were assessed in domains of attention (Hearts Cancellation test), language (Boston Naming Test), episodic memory (Logical Memory Test), working memory (Digit Span Backwards task), and executive functioning (set-shifting: Trail Making Test, Part B), as part of the OX-CHRONIC study, a longitudinal stroke cohort. Fatigue was assessed using the Fatigue Severity Scale. In a multiple linear regression analysis inclusive of above cognitive domains, only poorer executive functioning was associated with increased fatigue severity. This provides insight into the cognitive impairment profile of post-stroke fatigue long-term after stroke, with executive functioning deficits as the key hallmark.

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Chronic stroke; fatigue; domain-specific cognition; executive functioning

Introduction

Stroke is the second highest cause of death and the third leading cause of disability in the world (Feigin et al., 2022). There are currently 1.2 million stroke survivors in the United Kingdom, with approximately 100,000 individuals sustaining a new

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stroke each year (National Institute for Health and Care Excellence, 2019). Although improvements in acute stroke care have led to a decrease in mortality rates, the number of individuals living with long-term disabilities has risen (Johnson et al., 2019; Seminog et al., 2019). Less visible sequelae of stroke, including cognitive impairments and mood changes, have gained increasing attention in research due to their impact on post-stroke quality of life (e.g., Moore et al., 2021; Williams & Demeyere, 2021). Post-stroke fatigue has also been suggested to have a cumulative association with functional outcomes (van de Port et al., 2006).

Post-stroke fatigue (PSF) is one frequent and pervasive outcome, affecting between 25% and 85% of stroke survivors (Cumming et al., 2016). Of those with PSF, up to 40% of stroke survivors report it as their most impairing symptom (Ingles et al., 1999). Although no consensus has been reached for a definition of PSF, it is conceptualised as a persistent sense of physical or mental tiredness that does not subside with regular rest (Aarnes et al., 2020; De Doncker et al., 2018). Fatigue can be experienced in a variety of ways after stroke, including physical, cognitive, affective, or a combination thereof (Eilertsen et al., 2012; Skogestad et al., 2021; Wu et al., 2015). Despite the negative influence of PSF on rehabilitation, disability, and mortality (De Doncker et al., 2018; Lerdal et al., 2009), consistent factors contributing to its onset and maintenance remain poorly understood. Studies furthering our understanding of the underlying mechanisms of PSF has been rated as a top priority for future research by stroke survivors, carers, clinicians, and researchers (Watson et al., 2021).

Multiple factors have been linked to fatigue after stroke, such as demographic, biological, affective, and cognitive components (e.g., Aarnes et al., 2020; De Doncker et al., 2018; Ponchel et al., 2015; Wu et al., 2015). It is thought that different factors exert greater influence on fatigue severity at different time points in recovery. Wu et al. (2015) postulate that biological factors, such as stroke severity, lesion size, and stroke-induced neuroinflammation contribute to fatigue in the first several months after stroke. In contrast, psychosocial and behavioural factors are thought to perpetuate fatigue after this initial stage. In a recent conceptual model, Skogestad et al. (2021) propose that emotional difficulties, cognitively demanding tasks, and challenging activities in daily life aggravate fatigue severity in the chronic phase of stroke. Although cognitive impairments may contribute to fatigue levels in both the acute and chronic stage post-stroke recovery (Wu et al., 2015), the relationship between chronic fatigue and cognitive impairment is unknown. It is possible that over time stroke survivors build cognitive self-management strategies to reduce the impact on fatigue. However, in line with conceptual models (e.g., Skogestad et al., 2021), persistent cognitive impairments may aggravate chronic fatigue when stroke survivors aim to return to pre-stroke levels of function.

Of the myriad of factors that have been associated with PSF, its relationship with cognitive functioning has received relatively little empirical attention. This is surprising, given that cognitive impairment affects up to 91.5% of stroke

survivors (Jaillard et al., 2009). Qualitatively, stroke survivors with PSF report difficulties in making decisions, maintaining attention on tasks, and ignoring irrelevant stimuli in the environment (Eilertsen et al., 2012; Skogestad et al., 2021). This suggests that those with high levels of PSF may experience co-occurring cognitive impairments (Skogestad et al., 2021). However, quantitative research has reported mixed findings. A systematic review conducted by Lagogianni et al. (2018) identified 11 studies that examined the association between PSF and cognitive functioning, seven of which reported non-significant findings. The authors concluded that evidence is not sufficient to either support or refute an association between cognition and PSF, emphasising the need for further research.

Most studies examining the association between PSF and cognitive impairment have used domain-general measures of cognition, rather than examining the influence of specific cognitive domains to PSF severity. Among the studies included in the Lagogianni et al. (2018) review, the Mini Mental State Examination (MMSE; Folstein et al., 1975) was the most frequently used cognitive assessment tool. The MMSE is a global cognitive screen, developed for adults with dementia, and is considered to lack sensitivity in detecting cognitive changes post-stroke (Mancuso et al., 2018; Van Heugten et al., 2015). It is possible that cognitive functioning in specific domains may better explain PSF severity than global cognitive status. In a recent meta-analysis examining the association between fatigue severity and domain-specific cognitive impairment after acquired brain injury (ABI) including stroke, Dillon et al. (2022) found that higher fatigue levels were related to impaired information processing, attention, and to a certain extent, executive functioning and memory. The authors indicate the need for studies targeting domain-specific cognitive functions to identify more robust associations with fatigue after ABIs such as stroke.

In line with this, the "coping hypothesis" proposes that domain-specific cognitive changes explain the development of fatigue (Azouvi et al., 2004; Belmont et al., 2009; Jonasson et al., 2018; Staub & Bogousslavsky, 2001). Originally developed in traumatic brain injury (TBI) populations, the coping hypothesis states that fatigue is the result of the additional mental effort needed when maintaining normal levels of function on daily tasks. Impairments in the domains of attention, processing speed, and aspects of executive functioning such as working memory, are thought to be most strongly implicated in this process of producing fatigue (Azouvi et al., 2004; Belmont et al., 2009; Jonasson et al., 2018). Given that stroke is another type of ABI that can induce similar domain-specific cognitive impairments, the coping hypothesis may be relevant to the development of PSF (Dillon et al., 2022; Jonasson et al., 2018; Ponchel et al., 2015). However, it is unknown to what degree the tenets of the coping hypothesis hold true in adults experiencing PSF.

Of the studies that have examined domain-specific contributions to PSF, associations have been reported with attention and executive functioning (De Doncker & Kuppuswamy, 2022; Johansson & Rönnbäck, 2012; Kuppuswamy et al., 2022;

Radman et al., 2012; Ulrichsen et al., 2020), working memory (Hubacher et al., 2012), episodic memory (Graber et al., 2019; Pihlaja et al., 2014), and processing speed (Goh & Stewart, 2019; Hubacher et al., 2012; Johansson & Rönnbäck, 2012; Radman et al., 2012). However, these studies have been conducted primarily in early stroke. Few studies have investigated the relationship between domain-specific functioning and PSF more than two years post-stroke (i.e., Johansson & Rönnbäck, 2012; Kuppuswamy et al., 2022; Ulrichsen et al., 2020). Of these studies, only one has examined more than one cognitive domain in their analyses (Johansson & Rönnbäck, 2012). It may be the case that long-term post-stroke, when deficits in specific domains have persisted for some time, the influence of these impairments are more relevant to PSF than in earlier stages of recovery (Skogestad et al., 2021). Hence, research is needed to clarify the relationship between domain-specific cognitive functioning and PSF among chronic stroke survivors.

In this study, we aimed to evaluate the cognitive impairment profile associated with PSF in the chronic phase of post-stroke recovery. Given that the coping hypothesis suggests that impairments in attention and aspects of executive functioning, such as working memory, are relevant to PSF severity (Jonasson et al., 2018), we conducted a formal test of the relationship of functioning in these domains, compared to other types of cognitive impairment, to the severity of concurrent PSF in chronic stroke survivors. We hypothesised that poorer functioning in attention, working memory, and executive functioning, measured using a set-shifting task, would significantly relate to the severity of self-reported PSF.

Methods

Standard protocol approvals, registrations, and patient consents

This pre-registered study (https://osf.io/pskhx) is a secondary analysis of data collected as part of the observational cohort study OX-CHRONIC (NHS REC 19/SC/530; Demeyere et al., 2021; Kusec et al., 2023). All procedures were carried out according to the Declaration of Helsinki, and informed written consent was obtained from all participants.

Study design

The present investigation is a cross-sectional, observational study of OX-CHRONIC data.

Participants

OX-CHRONIC participants were recruited from the Oxford Cognitive Screening programme (Demeyere et al., 2015). Initial inclusion criteria for this study

were: (1) diagnosis of an acute stroke; (2) at least 18 years old; (3) ability to remain alert for 20 minutes; (4) ability to provide informed consent. The only exclusion criteria were inability to stay awake for more than 20 minutes and a lack of sufficient understanding of the English language (i.e., to understand task instructions). OX-CHRONIC participants consented to be re-contacted for research after completing the Oxford Cognitive Screening Programme. Those recruited for the OX-CHRONIC study ($N = 105$) compared to the initially recruited sample ($N = 761$) were younger at the time of stroke, had a higher number of years of education on average, and experienced lower levels of cognitive impairment. OX-CHRONIC participants did not differ from non-participants in terms of stroke severity, stroke type, or sex (Kusec et al., 2023). Those included in the OX-CHRONIC study were at least two years post-stroke at the time of assessment. Data collection for the measures included in this study took place between December 2020 and September 2021.

Procedure

Due to COVID-19 restrictions, data collection for OX-CHRONIC was carried out remotely, via telephone or videoconferencing. Of the 105 participants assessed, 79 completed assessments via telephone (75.23%) and 26 completed assessments via videoconferencing. We used Zoom to conduct videoconferencing sessions. Participants were sent a link to access their videoconferencing session prior to the testing date. Participants were posted testing booklets containing the self-report questionnaires, as well as the necessary visual stimuli to complete cognitive tasks remotely. These testing booklets were sent in sealed envelopes, and participants were instructed not to open materials until told to do so by the tester. Assessments took place over two testing sessions, with each session lasting approximately 45 minutes. Specific instructions were given to participants over the phone or via videoconferencing on how to complete each task. Participants were advised to sit in a quiet environment and to minimise any noise from external stimuli such as the radio or television. Participants were further instructed not to write any information down during the testing session. Participants were encouraged to attempt all tests. Any issues impeding test completion, such as motor, sensory, or language difficulties, were communicated to the tester during the testing session and mitigations were put in place where possible (e.g., by using the non-affected hand for the Trail Making Test, Part B, or by having a carer present to help with communication). However, participants were not excluded for any motor, sensory, or language difficulties other than the main exclusion criteria of sufficient language understanding. After the testing sessions, participants placed their testing booklets in a prepaid envelope, which they then posted to the OX-CHRONIC team for scoring and data entry. Demographic and clinical information was obtained from participants' medical records, with consent.

Further details pertaining to data collection has been published in the OX-CHRONIC protocol (Demeyere et al., 2021; Kusec et al., 2023).

Measures

Several self-report questionnaires and neuropsychological assessments of cognitive functioning were administered to participants as part of the OX-CHRONIC protocol (Demeyere et al., 2021). Measures pertaining to the current study are described below.

Self-reported fatigue

Self-reported fatigue was measured using the *Fatigue Severity Scale* (FSS; Krupp, 1989). This is a 9-item scale used in several neurological populations including stroke (Whitehead, 2009). Items are rated on a 7-point Likert scale, ranging from Strongly Disagree (1) to Strongly Agree (7). Total scores on this scale range from 7 to 63. To calculate the average FSS score, the total score is divided by the number of items to which the participant has responded. A cut-off score of 4 or greater is most frequently used to describe clinically significant fatigue (Cumming et al., 2016). This cut-off was used to describe the prevalence of significant fatigue in the current sample. The FSS has good reliability and validity in measuring post-stroke fatigue (Ozyemisci-Taskiran et al., 2019).

Domain-specific cognition: In-depth assessment

Executive functioning: Set-shifting. The *Trail Making Test, Part B* (Reitan, 1992) was used to measure executive functioning in this study. This test is designed to assess the ability to switch between different sets of information, thereby measuring the *set-shifting* component of executive functioning (Muir et al., 2015). We pre-registered to use this executive functioning measure from the OX-CHRONIC testing battery (Demeyere et al., 2021) so as to have one measure per cognitive domain. The Trail Making Test, Part B was chosen from other executive functioning measures, given that performance in this test is unlikely to be unduly influenced by language abilities. Participants are shown an array of numbers (1–25) and letters (A–L) dispersed on an A4 page. Participants are instructed to begin at number 1 and draw a line alternating between numbers and letters in ascending order. Accuracy scores on this task were used to measure set-shifting abilities. Accuracy scores are calculated by counting the number of correct set shifts, ranging from 0 to 23. Though the time taken to complete the Trail Making Test is often used as an index of performance on this task (Bowie & Harvey, 2006), we chose to use accuracy scores instead, as remote testing made it difficult to capture precise time estimates. Further, assessing set-shifting abilities by measuring the total time taken to complete this task may incorrectly assign individuals with imperfect accuracy as having non-impaired set-shifting, if they completed the task

quickly. Prior research indicates that the Trail Making Test is a reliable and valid measure of executive functioning (e.g., Fals-Stewart, 1992; Sánchez-Cubillo et al., 2009).

Working memory. Working memory was assessed using the *Digit Span Backward* task of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981). Participants are instructed to repeat a sequence of numbers in the reverse order of that read aloud by the assessor. Number sequences increase in length as the task progresses. Two different number sequences are read aloud for each number sequence length. If incorrect answers are given for both sequences, the task is discontinued. Scores range between 0 and 12 on this task. The Digit Span Backwards task is a frequently used measure of working memory function after stroke (e.g., Lugtmeijer et al., 2021).

Attention. The *Hearts Cancellation* subtest of the OCS was used to assess selective and spatial attention. This task presents participants with an A4 sheet of paper containing 150 line drawings of hearts. Of these 150 hearts, 50 contain a right-sided gap, 50 contain a left-sided gap, and 50 do not have a gap. Participants are given three minutes to cross out all the complete hearts on the page, whilst ignoring incomplete hearts. Accuracy scores on this task are calculated by counting the number of complete hearts correctly crossed-out by participants, irrespective of whether the participant also crossed out hearts with gaps. Although the Hearts Cancellation test is primarily a measure of spatial attention, this accuracy score thus also reflects selective attention abilities. This accuracy score (ranging from 0 to 50) was used to represent attentional functioning in the current study.

Pre-registered covariates

The below measures were used as covariates when examining the relationship between cognitive impairment and PSF:

Episodic memory. The *Logical Memory Test – Part 2* of the Wechsler Memory Scale-Revised (Wechsler, 1981) was used to assess episodic memory. A short prose passage is read aloud by the assessor. Participants are instructed to recall as many details from this passage as they can remember, after a delay of approximately 30 minutes. Total scores vary from 0 to 25, representing the number of sections of the passage that were correctly recalled by participants. The Logical Memory Test is a well-established, valid, and reliable test of episodic memory functioning (Larrabee et al., 1985; Sullivan, 1996).

Language. Language was assessed using the short version of the *Boston Naming Test* (Mack et al., 1992). Participants are presented with drawings of 15 different objects and asked to name each one. Stimulus and phonemic cues are given to participants to assist with naming as needed. Accuracy scores, ranging from 0-15, represent the number of objects correctly named without cues. This test has well-established reliability and validity (Ferraro & Lowell, 2010).

Depressive symptoms. Depressive symptoms were assessed using the *Hospital Anxiety and Depression Scale-Depression Subscale* (HADS-D; Zigmond & Snaith, 1983). This subscale consists of 7 items rated on a Likert scale from 0-3. Total HADS-D scores range from 0-21, with higher scores representing more severe depressive symptoms. The HADS is used extensively in clinical practice and research (Bjelland et al., 2002). It has demonstrated high sensitivity and specificity in detecting post-stroke depression (Prisnie et al., 2016).

Acute stroke severity. Stroke severity was assessed acutely by medical professionals using the *National Institute of Health Stroke Scale* (NIHSS; Brott et al., 1989). NIHSS scores were obtained from acute medical records with consent. The NIHSS consists of 11 items, measuring stroke-related cognitive and motor deficits. Scores on this scale range from 0-42, with higher scores representing greater stroke severity.

Domain-specific cognition: Brief assessment

Domain-specific cognitive impairment was also assessed using a brief measure of cognitive functioning; the Oxford Cognitive Screen (OCS; Demeyere et al., 2015; 2016). The OCS is a domain-specific and aphasia-friendly cognitive screening tool, designed specifically for stroke survivors. A remote adaptation of the OCS was used for the OX-CHRONIC study. This Tele-OCS was recently validated (Webb et al., 2023) and consists of 10 subtests and assesses cognitive functioning in five domains: attention, executive functioning, episodic memory, language, and number processing. Scores on each subtest were binarized into impairment scores (0 = unimpaired, 1 = impaired), based on normative data (Demeyere et al., 2015). A domain on the OCS is considered impaired if at least one subtest in that domain is impaired.

Sample size

This study is a secondary analysis of existing data. For this reason, the sample size ($N = 105$) was determined prior to the formulation of the study hypothesis. 90 of 105 participants had complete data across all variables of interest and were included in the main analysis. Using the *pwr* package in R (Champely, 2020), a sample of 90 participants with an alpha of 0.05 had 93% power to detect an effect size of 0.25.

Statistical analyses

All analyses were carried out using R version 4.1.2 (R Core Team, 2021). Basic descriptive statistics were carried out across all study variables. This was followed by a series of correlational analyses investigating the association between participants' scores on the FSS and each variable included in the

main regression analysis. Data were checked to ensure that the assumptions of linearity, homoscedasticity of residuals, normally distributed residuals, and low multi-collinearity among predictor variables were met. Predictor variables of interest were cognitive functioning in the domains of attention (Hearts Cancellation subtest), executive functioning (Trail Making Test, Part B), and working memory (Digit Span Backward task). Covariates were age, sex, time since stroke, stroke severity (NIHSS scores), and depressive symptoms (HADS-D scores). Cognitive functioning in the domains of episodic memory (Logical Memory Test, Part 2) and language (Boston Naming Test, short version) were additionally entered as covariates to determine if the domains of attention, executive function, and working memory were *uniquely* associated with greater fatigue severity. We used participants' raw scores on cognitive tests in all statistical analyses. A Bonferroni correction was applied to *p*-values to correct for the increased risk of obtaining a Type 1 error due to multiple comparisons. We report on results with and without Bonferroni corrections for multiple comparisons.

Missing data

Missing observations were imputed using multiple imputation via predictive mean matching (PMM) using the *mice* package in R (van Buuren & Groothuis-Oudshoorn, 2011). This was conducted across five versions of an imputed dataset with a maximum of 50 iterations. The main analysis was re-conducted across these five imputations and pooled into a single estimate. This pooled estimate was compared to the results of the complete case analysis. Hawkin's test of Normality and Homoscedasticity was performed prior to multiple imputation to determine whether data were Missing Completely at Random, Missing at Random, Missing Not at Random. Multiple imputation has gained increasing recognition as a reliable technique for handling datasets with missing observations (Austin et al., 2021), and has been shown to yield accurate statistical inferences across a range of different sample sizes with different proportions of missingness (Kleinke, 2018). 15 participants had missing data for at least one variable of interest, in most cases for NIHSS scores. Full details on the proportion and type of missingness across study variables are included in the Supplementary Materials.

Results

Participant characteristics

Participants (41.90% female) had an average age of 72.92 years ($SD = 13.01$) and were approximately 4.57 years ($SD = 2.12$) post-stroke. Full participant clinical and demographic information is displayed in Table 1.

Table 1. Participant characteristics. NIHSS data were available for 85 participants. HADS-D data were available for 98 participants. Full data were available for all other variables. HADS-D = Hospital Anxiety and Depression Scale – Depression. NIHSS = National Institute of Health Stroke Scale.

Participants ($N = 105$)		Min–Max
Sex – *n* (%)		
Male	61 (58.10%)	
Female	44 (41.90%)	
Age – Mean (*SD*)	72.92 (13.01)	22–97
Education (years) – Mean (*SD*)	14.06 (4.01)	9–28
Stroke Laterality		
Right Hemisphere	41 (39.05%)	
Left Hemisphere	42 (40.00%)	
Bilateral	8 (7.60%)	
Undetermined from scan	14 (13.35%)	
Stroke type		
Ischaemic	88 (83.80%)	
Haemorrhagic	17 (16.20%)	
Time post-stroke (years) – Mean (*SD*)	4.57 (2.12)	2–9.38
NIHSS – Mean (*SD*)	7.39 (6.25)	0–27
HADS-D – Mean (*SD*)	4.97 (3.98)	0–21

Prevalence of fatigue

The mean FSS score was 3.95 ($SD = 1.70$). 52 of 101 participants (51.49%) had FSS scores greater than or equal to 4 and were classified as having clinically significant fatigue (see Figure 1 for FSS distribution).

Domain-specific cognition

Participants' mean scores in the domains of attention (Hearts Cancellation subtest), executive functioning (set-shifting: Trail Making Test, Part B), and working memory (Digit Span Backward task) were 43.53 ($SD = 7.88$), 18.54 ($SD = 6.00$), and 5.90 ($SD = 2.14$).

Correlational analyses

Average FSS scores were significantly correlated with HADS-D scores ($r = 0.45$, $p < .001$), Accuracy scores on the Hearts Cancellation subtest ($r = -0.23$, $p = .03$) and Accuracy scores on the Trail Making Test, Part B ($r = -0.28$, $p = .006$). After adjusting the alpha level to 0.005 with a Bonferroni correction (0.05/10 tests), only the average between FSS scores and HADS-D scores remained significant. These correlations are displayed in the Supplementary Materials.

Association between fatigue severity and domain-specific cognitive functioning

A multiple linear regression was conducted to investigate the association between fatigue severity (FSS scores), and cognitive functioning in the domains of attention

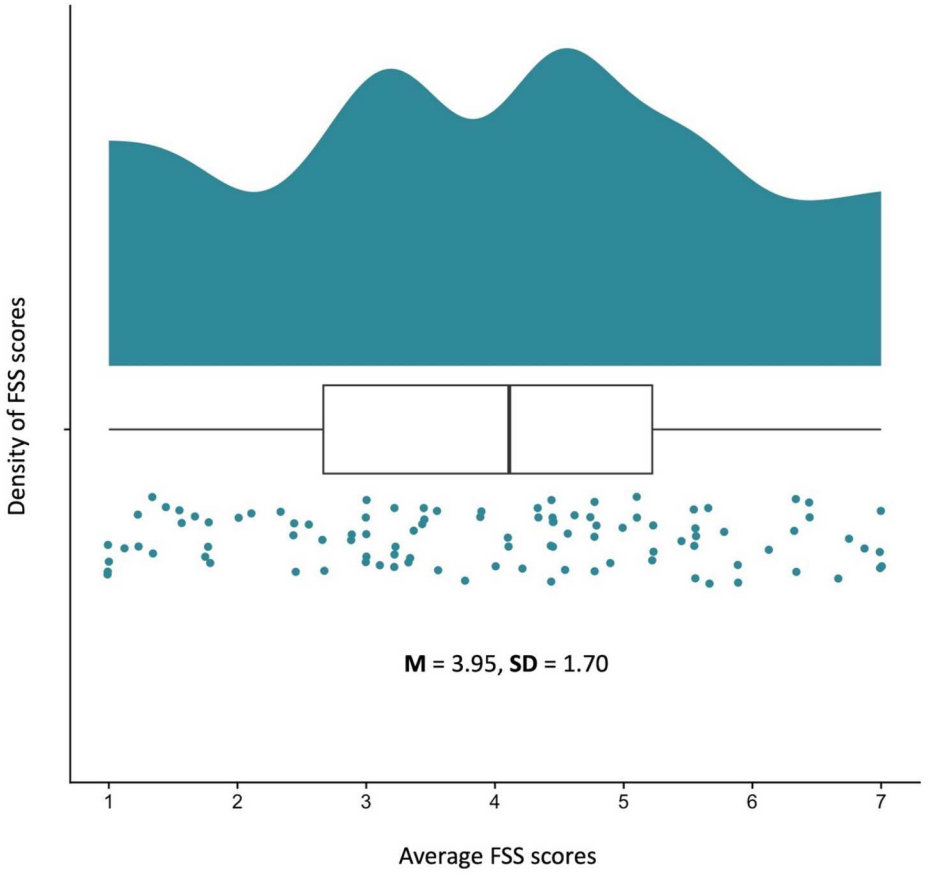

Figure 1. Distribution of Fatigue Severity Scale scores among chronic stroke participants. Minimum score = 1, Maximum score = 7. Clinically relevant fatigue defined as FSS scores ≥ 4. Vertical line within boxplot represents a median value of 4.11. FSS = Fatigue Severity Scale; **M** = Mean; **SD** = Standard Deviation.

(Hearts Cancellation subtest), executive functioning (set-shifting: Trail Making Test, Part B), and working memory (Digit Span Backward task). The covariates included in the model were age, sex, time since stroke, depressive symptoms (HADS-D scores) and cognitive functioning in the domain of episodic memory (Logical Memory Test, Part 2). Stroke severity (NIHSS scores) was excluded as a covariate from the final analyses due to the large proportion of missing data in this variable (19.04%). Cognitive functioning in the domain of language (the Boston Naming Test) was removed as a covariate due to its highly skewed variance making main regression results uninterpretable. Notably, neither NIHSS scores nor the Boston Naming Test were independently associated in a univariate regression with FSS scores (see correlations in Supplementary Materials where these excluded covariates are discussed in further detail).

Influential cases in this model were identified with Cook's Distance. Six data points had a Cook's Distance value greater than three times the mean Cook's

Distance value and were excluded from the main analysis. This final model ($N = 84$) was significant, $F_{(8, 75)} = 4.99$, $p < .001$, $R^2 = 0.35$, Adj, $R^2 = 0.28$. Of the predictor variables of interest, only Accuracy scores on the Trail Making Test, Part B was significantly associated with participants' FSS scores ($B = -0.10$, 95% CI [−0.16, −0.03], $SE = 0.03$, $p = .005$). Of the covariates, only HADS-D scores ($B = 0.19$, 95% CI [0.11, 0.28], $SE = 0.04$, $p < .001$) was an additional significant predictor of FSS scores.

Main analysis using multiple imputation

The main regression analysis was re-conducted across five versions of an imputed dataset, excluding the six outliers identified with Cook's Distance. As in our complete-case analysis, regressions in each of these five imputations ($N = 99$) were significant ($ps < .001$, pooled $R^2 = 0.35$). The Trail Making Test, Part B (B range = −0.09 – −0.07, $SE = 0.03$ across all datasets) and the HADS-D (B range = 0.17–0.21, $SE = 0.04$ across all datasets) were significantly associated with FSS scores in each imputed dataset. In one dataset, The Logical Memory Test, Part 2 also emerged as a significant predictor of FSS scores ($B = -0.07$, 95% CI [−0.13, −0.004], $SE = 0.03$, $p = .04$). Table 2 compares the pooled results of these five imputations to complete case analysis.

Exploratory analysis: Association between fatigue severity and Oxford Cognitive Screen scores in chronic stroke survivors

An exploratory analysis was conducted to examine whether domain-specific cognitive impairments detected using the Oxford Cognitive Screen (OCS)

Table 2. Summary of multiple linear regression analysis with and without imputations for missing observations. Imputed values are the results obtained across five versions of an imputed dataset. Executive Functioning (set-shifting) was measured using the Trail Making Test, Part B. Attention was measured using the Hearts Cancellation subtest. Working Memory was measured using the Digit Span Backwards task. Episodic Memory was measured using the Logical Memory Test, Part 2. B = coefficient weights; SE = standard errors; HADS-D = Hospital Anxiety and Depression Scale – Depression.

	Dependent Variable: FSS scores					
	With complete cases ($N = 84$)			With imputations for variables with missing cases ($N = 99$)		
	B	*SE*	*t*	*B*	*SE*	*t*
Cognitive predictors						
Executive Functioning	−0.10	0.03	**−2.92***	−0.08	0.03	**−2.50***
Attention	0.03	0.02	1.41	0.03	0.02	1.26
Working Memory	0.05	0.08	0.67	0.04	0.08	0.44
Covariates						
Episodic Memory	−0.04	0.03	−1.22	−0.05	0.03	−1.35
HADS-D	0.19	0.04	**4.38****	0.19	0.04	**4.73****
Age	0.01	0.01	0.68	0.004	0.01	0.35
Sex	−0.42	0.31	−1.38	−0.29	0.30	−0.96
Time Since Stroke	0.03	0.07	0.47	0.03	0.07	0.48

*$p < .05$, **$p < .001$.

were associated with fatigue severity in the OX-CHRONIC cohort. This was carried out to elucidate whether a *brief* screen of domain-specific cognition would be informative in explaining concurrent symptoms of fatigue among chronic stroke survivors.

A multiple linear regression was conducted using complete cases ($N = 88$) with HADS-D scores, age, sex, and time since stroke as covariates. This model was significant ($F_{(9,\ 78)} = 3.59$, $R^2 = 0.29$, Adj $R^2 = 0.21$). Cognitive impairment in the domains of executive functioning ($B = 1.34$, $SE = 0.64$, $p = 0.04$, CI [0.07, 2.60]) and episodic memory ($B = 1.84$, $SE = 0.72$, $p = 0.01$, CI [0.41, 3.27]) were significantly associated with FSS scores. HADS-D scores were also significantly associated with FSS scores ($B = 0.16$, $SE = 0.05$, $p < .001$, CI [0.07, 0.25]). After correcting for multiple comparisons with a Bonferroni correction to account for the main analysis and exploratory analysis, executive functioning no longer remained a significant predictor of FSS scores.

This analysis was re-conducted using multiple imputation for missing data across five versions of an imputed dataset. The final model ($N = 105$) was significant in each of these imputations ($ps < .001$, pooled $R^2 = 0.30$). Executive functioning (B range = 1.07–1.37, SE range = 0.45–0.52) was a significant predictor of FSS scores in all five imputations. Episodic memory was a significant predictor of FSS scores in four out of five imputations (B range = 0.81–1.61, SE range = 0.53–0.61). The HADS-D (B range = 0.15–0.18, $SE = 0.04$ across all datasets) significantly predicted FSS scores in each imputation. The pooled results of these five imputations are compared to the complete case analysis in Table 3. Figure 2 displays the relationship between executive functioning impairment and FSS scores and Figure 3 displays the relationship between episodic memory impairment and FSS scores (both using complete cases).

Table 3. Summary of the exploratory multiple linear regression analysis with and without imputations for missing observations. Cognitive predictors were measured using the Oxford Cognitive Screen (OCS). Imputed values are the results obtained across five versions of an imputed dataset. B = coefficient weights; SE = standard errors; HADS-D = Hospital Anxiety and Depression Scale – Depression.

	Dependent Variable: FSS scores					
	With complete cases ($N = 88$)			With imputations for variables with missing cases ($N = 105$)		
	B	*SE*	*t*	*B*	*SE*	*t*
OCS cognitive predictors						
Executive functioning	1.34	0.64	**2.10***	1.23	0.51	**2.39***
Attention	−0.12	0.44	−0.27	−0.30	0.40	−0.75
Episodic memory	1.84	0.72	**2.56***	1.27	0.65	1.94
Language	−0.22	0.55	−0.41	−0.13	0.52	−0.25
Number processing	−0.42	0.54	−0.77	−0.41	0.50	−0.82
Covariates						
HADS-D	0.16	0.05	**3.52****	0.16	0.04	**3.96****
Age	0.01	0.01	0.93	0.01	0.01	0.53
Sex	−0.37	0.34	−1.10	−0.35	0.32	−1.10
Time since stroke	−0.08	0.08	−0.995	−0.03	0.08	−0.45

*$p < .05$, **$p < .001$.

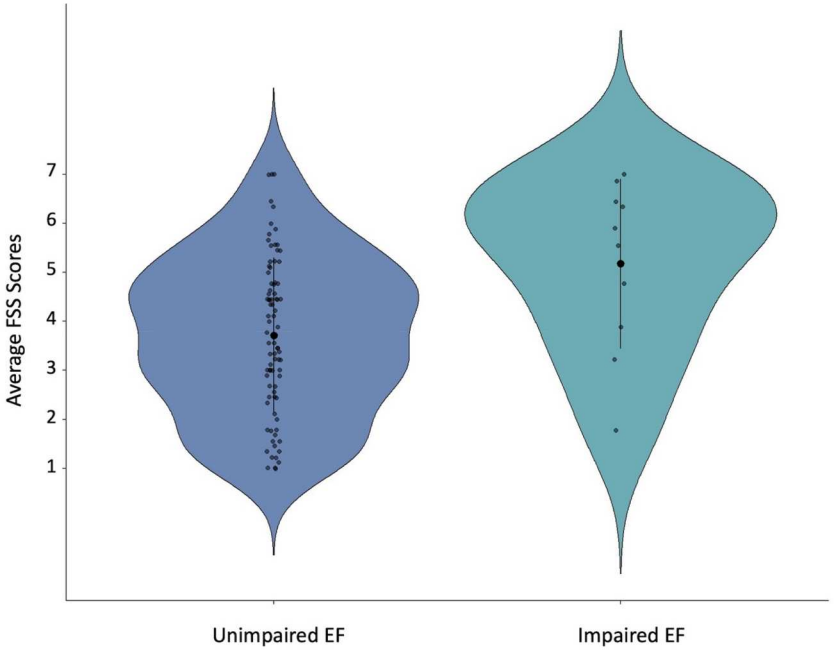

Figure 2. Relationship between Fatigue Severity Scale scores and executive functioning impairment scores. Means and standard deviations are presented (in black) along with individual participant scores. FSS = Fatigue Severity Scale; EF = Executive Function.

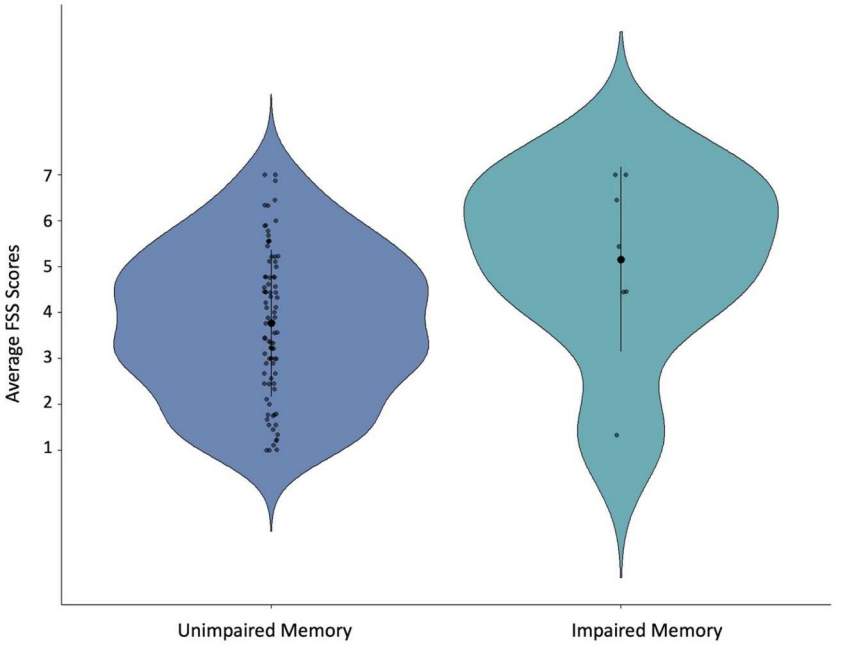

Figure 3. Relationship between Fatigue Severity Scale scores and episodic memory impairment scores. Means and standard deviations are presented (in black) along with individual participant scores. FSS = Fatigue Severity Scale.

Discussion

This study aimed to investigate the cognitive impairment profile of chronic PSF. In a sample of 105 stroke survivors, poorer executive functioning, measured using a set-shifting task, was associated with greater PSF severity. This suggests that executive functioning deficits, specifically set-shifting difficulties, are linked with higher levels of fatigue in chronic stroke survivors, than those who are less impaired in this domain. In the present sample, 51.49% of participants experienced clinically significant fatigue, similar to prior studies investigating PSF prevalence (Cumming et al., 2016).

Domain-specific cognitive functioning in chronic PSF

As hypothesised, poorer performance in the domain of executive functioning, specifically set-shifting abilities, was related to concurrent fatigue severity in this chronic stroke cohort. This is consistent with prior research reporting executive dysfunction among chronic stroke survivors (Johansson & Rönnbäck, 2012; Radman et al., 2012). The current findings also lend support to the utility of the coping hypothesis in understanding PSF (Azouvi et al., 2004; Belmont et al., 2009; Dillon et al., 2022; Jonasson et al., 2018). It is possible that individuals with chronic executive function difficulties experience fatigue due to the compensatory effort required to maintain performance on everyday tasks. These results provide insight into a potential factor associated with the pervasive nature of fatigue after stroke.

The present study further demonstrates that the set-shifting component of executive functioning is *uniquely* associated with PSF severity when controlling for cognitive functioning in other domains. Executive functioning is a higher-level cognitive ability which directs performance in a wide range of activities requiring attentional control, simultaneous task completion, and decision-making (Cristofori et al., 2019). Evidence from qualitative research demonstrates that those living with PSF find it difficult to make decisions, maintain concentration on specific tasks, and ignore irrelevant stimuli in their environment (Eilertsen et al., 2012; Skogestad et al., 2021). These everyday activities that stroke survivors find fatigue-inducing are also ones which appear to be dependent upon executive functioning abilities. Given the wide-reaching impact of executive dysfunction on multiple areas of everyday life, it is perhaps unsurprising that this domain is uniquely related to chronic PSF.

In our exploratory analysis, PSF severity was related to impairments in the OCS domains of executive functioning and episodic memory. This provides support for the main analysis, indicating that executive functioning impairments, specifically set-shifting, detected using a brief cognitive screen may be informative in understanding elevated fatigue levels after stroke. The finding that PSF severity also relates to episodic memory impairments on the OCS is

in line with prior research (Graber et al., 2019; Pihlaja et al., 2014). However, it should be noted that we did not find an association between episodic memory and PSF using a more in-depth assessment (Logical Memory Test, Part 2) in our main analysis, nor was this a hypothesized predictor relevant to PSF. Thus, this finding should be interpreted with caution and replicated in independent samples.

Contrary to our hypotheses, neither attention, nor working memory significantly related to PSF severity. This is inconsistent with prior research reporting a relationship between PSF levels and functioning in these domains (De Doncker & Kuppuswamy, 2022; Hubacher et al., 2012; Johansson & Rönnbäck, 2012; Kuppuswamy et al., 2022; Radman et al., 2012; Ulrichsen et al., 2020). We note that the measures used to assess attention and working memory in the current investigation differ from that of prior research. Previous studies reporting a significant association between fatigue and attentional impairments assessed attention via *sustained* attentional functioning tasks (Johansson & Rönnbäck, 2012; Radman et al., 2012; Ulrichsen et al., 2020). Recent meta-analytic evidence further suggests that cognitive tasks requiring sustained effort place extraneous demands on stroke survivors' reduced attentional resources, giving rise to feelings of fatigue (Dillon et al., 2022). The Hearts Cancellation test employed in the present investigation primarily reflects selective and spatial attention abilities post-stroke (Demeyere et al., 2015). It is thus possible that impairments in this type of attention are less relevant to the experience of PSF. The present investigation also employed a different measurement of working memory than previous studies. Hubacher et al. (2012) found that PSF related to performance on the Paced Auditory Serial Attention Task (PASAT; Gronwall & Sampson, 1974). The PASAT requires sustained performance for a longer period of time than the Digit Span Backwards task. One possibility is that the relatively brief assessment times needed for the Hearts Cancellation and Digit Span Backwards tasks, compared to longer sustained attention measures, are not sufficient to induce fatigue. Therefore, fatigue may be particularly present when attempting to maintain *sustained* performance on longer tasks requiring attention and working memory (Dillon et al., 2022; Skogestad et al., 2021).

Relationship of depressive symptoms to PSF

Depressive symptoms were significantly related to fatigue severity among chronic stroke survivors in the present study. This finding is consistent with a large body of literature reporting a positive association between depression and fatigue levels after stroke (e.g., Aarnes et al., 2020; Paciaroni & Acciarresi, 2019; Ponchel et al., 2015; Wu et al., 2015). This result is perhaps expected, given PSF and post-stroke depression share overlapping symptoms (e.g., lowered motivation, mental exhaustion that does not subside with rest; Aarnes et al., 2020). It is well-documented that fatigue and depression, although

related to each other, are also independent sequela of stroke (Park et al., 2009; van der Werf et al., 2001). The current findings support this idea, demonstrating unique associations between PSF and other factors (e.g., executive dysfunction) after controlling for the influence of depressive symptoms. Nevertheless, depressive symptoms may be an important treatment target in reducing PSF severity at the chronic phase of stroke.

It is possible that depression and cognitive impairments following stroke have different mechanisms to producing fatigue. In previous research, post-stroke depression has been consistently related to increases in fatigue (e.g., Galligan et al., 2016; Zhang et al., 2020). Further, elevated fatigue is a symptom of depression, thus an a priori relationship likely exists in chronic stroke survivors (Aarnes et al., 2020). It is also possible that executive function and depression interact in producing fatigue – previous models of PSF note that it is a multifaceted phenomenon that is affected by multiple biological, environmental, and psychological factors (Ponchel et al., 2015; Wu et al., 2015) and therefore there may be mediating pathways between fatigue, depression, and executive functioning. Of note, however, we find only a weak non-significant correlation between depression and set-shifting abilities here ($r = 0.18$). Investigations that further elucidate the relationship between emotion, cognition, and fatigue post-stroke would be of benefit.

Limitations

As this study was a secondary analysis of an existing dataset, our sample was limited to those who had available data at the investigated time point. Furthermore, participants were not excluded from this study if they had a previous stroke, or other neurological or psychiatric diagnoses. It is possible that such pre-existing conditions impacted the cognitive performance and fatigue scores in the participants affected by them. However, it should also be acknowledged that these broad inclusion criteria allowed for a representative sample of the broader stroke population, increasing the generalisability of study findings. It should also be noted that the FSS may not accurately capture the multidimensional experience of fatigue among stroke patients (Mead et al., 2007). Although this scale has been validated in stroke (Ozyemisci-Taskiran et al., 2019), and is one of the most frequently used tools to measure PSF (Cumming et al., 2016), there are no items on the FSS which address mental fatigue, a well-established aspect of PSF (e.g., Eilertsen et al., 2012; Wu et al., 2015). This may have implications for identifying relationships between fatigue and cognitive assessments. It is worth noting that the relationship of processing speed to fatigue was not investigated, given the remote cognitive assessment methods employed here. Prior research has found slowed processing speed among those with PSF (Goh & Stewart, 2019; Hubacher et al., 2012; Johansson & Rönnbäck, 2012; Radman et al., 2012), and the coping hypothesis postulates that deficits

in processing speed influence fatigue severity (Azouvi et al., 2004; Belmont et al., 2009; Jonasson et al., 2018). Prospective studies of the relationship of domain-specific cognitive functioning to PSF should include measures of processing speed. Finally, episodic memory was assessed using the WMS-R version of the Logical Memory Test, rather than the most up to date WMS-IV.

The current findings have implications for clinical practice. Evidence-based treatments for PSF are lacking, partly due to our paucity of knowledge on its causative and maintaining mechanisms (Acciarresi et al., 2014; Wu et al., 2015). The present investigation indicates that poorer executive functioning abilities are independently associated with chronic PSF severity. It is possible that targeting these impairments in treatment could potentially alleviate symptoms of PSF severity among chronic stroke survivors. The present findings can also guide future research on the cognitive underpinnings of PSF. To better understand the temporal relationship between PSF and domain-specific cognitive functioning, prospective, longitudinal studies are needed that evaluate whether changes in executive functioning relates to changes in fatigue over time post-stroke. Additionally, it is worth investigating whether specific aspects of executive function may be of particular relevance to the experience of chronic PSF. Executive functioning encompasses a broad range of skills, including set-shifting, inhibitory control, and future-planning (Cristofori et al., 2019). Here, we find evidence of set-shifting abilities to PSF, though of note we find no unique relationship of working memory, a commonly considered element of executive functioning, to PSF. It may be the case that other executive function processes, beyond set-shifting and working memory, are differentially associated with fatigue levels in chronic stroke. Future research that employs a broad range of executive functioning measures, and other domain-specific cognitive assessments, are warranted in understanding how cognitive functioning relates to fatigue in chronic stroke.

Conclusion

In chronic stroke, poorer executive functioning abilities, measured using a set-shifting task, were associated with increased fatigue severity. This suggests that persistent executive functioning impairments have the potential to aggravate fatigue severity during longer-term recovery. Interventions that target executive dysfunction may be useful in alleviating symptoms of fatigue among long-term stroke survivors.

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Data availability statement

All data produced in this study are available online at https://osf.io/y2mev/.

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