Title:

Perceived Fatigue Change and Cognitive Performance Change in Multiple Sclerosis: Uncovering Predictors Beyond Baseline Fatigue

Short title: Drivers of perceived fatigue and cognitive performance change in MS

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Introduction

Fatigue is common in multiple sclerosis (MS), with up to 92% of patients identifying it as one of the most prevalent and problematic symptoms (Branas et al. , 2000). It has been reported as gender invariant (Bakshi, 2003, Flachenecker et al. , 2002) and has debilitating effects on physical function, activities of daily living (including employment and productivity), social relationships, psychological wellbeing, and quality of life (Bol et al. , 2009, Janardhan and Bakshi, 2002, Krause et al. , 2013, Krupp, 2003). The human and economic costs of fatigue indicate clear benefits in identifying and treating factors that contribute to its severity (Bol, Duits, 2009).

A variety of direct and indirect factors are believed to influence fatigue with the former comprising a range of biological disease characteristics (Braley and Chervin, 2010, Kos et al. , 2008, Tartaglia et al. , 2004) and the latter factors such as sleep, pain, mood, self-efficacy, and medications (Kos, Kerckhofs, 2008, Krupp et al. , 2005, Skerrett and Moss-Morris, 2006, Strober and Arnett, 2005). An understanding of fatigue in MS requires appreciation of the interaction of multiple mechanisms (Kos, Kerckhofs, 2008, Strober and Arnett, 2005).

Adding to the challenge are variable definitions of fatigue in MS (Braley and Chervin, 2010, Kos, Kerckhofs, 2008) with the literature historically conceptualising fatigue as a unitary construct and as a multifactorial symptom (Brassington and Marsh, 1998, Elkins et al. , 2000, Kos, Kerckhofs, 2008). Using a more recent classification (Kluger et al. , 2013); MS Fatigue may be conceptualised as *perceived fatigue*; a lack of motivation or a sense of tiredness that makes it difficult to efficiently perform daily physical and cognitive tasks (Aldughmi et al. , 2017, Finsterer and Mahjoub, 2014, Kluger, Krupp, 2013), and *performance fatigability*; a measure of change in the performance of a physical or a cognitive task over time (Enoka and Duchateau, 2016, Kluger, Krupp, 2013).

Studies examining perceived fatigue have shown variable links with disease characteristics, performance change and cognitive dysfunction (Biberacher et al. , 2018, Pierce, 1995, Wessely et al. , 1999). Further, the relationships between perceived fatigue and physical disability as measured using

the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) have been inconsistent (Bakshi et al. , 2000, Biberacher, Schmidt, 2018, Ghajarzadeh et al. , 2013). Whilst some links between perceived fatigue and motor performance fatigability have been demonstrated (Loy et al. , 2017, Skurvydas et al. , 2011, Zijdewind et al. , 2016), it has been suggested that perceived fatigue may be more closely associated with mood than neurological impairment (Bakshi, Shaikh, 2000).

An increasing drive to examine cognitive performance fatigability in MS has demonstrated that people with MS are vulnerable to cognitive performance change (Berard et al. , 2018, Cehelyk et al. , 2018, Claros-Salinas et al. , 2013, Krupp and Elkins, 2000, Wolkorte et al. , 2015). However, similarly to our understanding of perceived fatigue, the factors influencing cognitive performance change remain unclear. Although some recent studies (Aldughmi, Bruce, 2017, Cehelyk, Harvey, 2018, Wolkorte, Heersema, 2015) have demonstrated a relationship between perceived fatigue and cognitive performance fatigability, these have been analysed alongside concurrent motor tasks, and measurement of the multiple direct and indirect influences on fatigue has been inconsistent. Uncovering the predictors of perceived fatigue and cognitive performance fatigability is vital given their links with both physical and cognitive dysfunction (Bol, Duits, 2009, Elkins, Krupp, 2000). The implications for clinical practice are clear considering patients' physical, psychological and cognitive performance on testing may well influence treatment decisions.

We aimed to investigate the relationship between perceived fatigue and cognitive performance fatigability, and whether these are differentially influenced by physical disability, psychological factors and cognitive function in MS, using assessments relevant to clinical practice. We tested the hypothesis that perceived fatigue is predicted by indirect factors, such as mood, sleep and pain. In contrast, we hypothesised that cognitive performance fatigability is predicted by physical disability and cognitive function.

Methods

Participants

We utilised a cross sectional study design, selecting a cohort of individuals with adult-onset MS from a regional database of Neuroinflammatory patients in South Wales, United Kingdom (Hirst et al. , 2009). Opt-in letters were sent, and prospective participants were further screened over the telephone. Compliance with inclusion/exclusion criteria was gauged via medical records and interview during the screening calls. Inclusion criteria included; clinically definite diagnosis of MS within the last eight years; aged between 16-65 years old; and being fluent in English. The exclusion criteria included; history of other diagnosed neurological or psychiatric condition; taking drugs known to substantially impact on cognition and/or fatigue (e.g. baclofen); and having received a course of corticosteroids or disease modifying drugs within three months of recruitment. The study was approved by the Cardiff and Vale University Health Board Ethics Committee (ref no. 05/WSE03/111).

Measures and Design

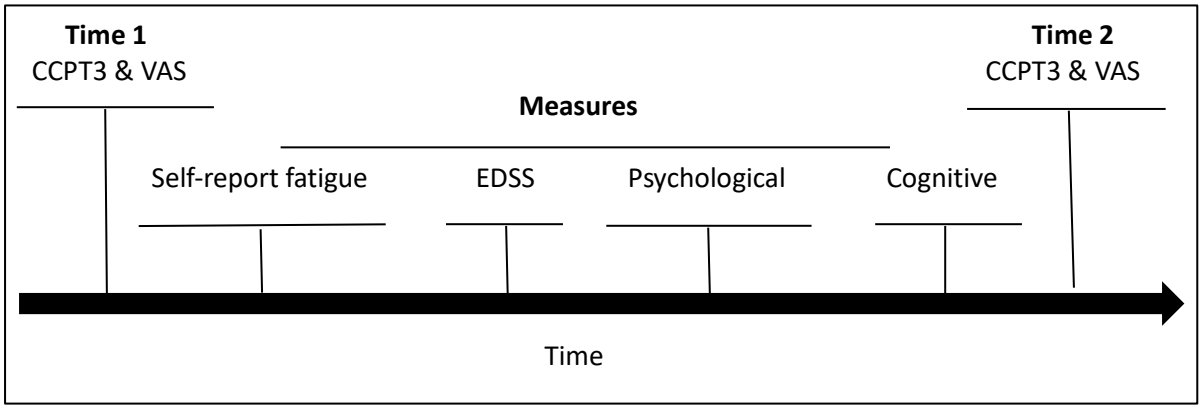
The Modified Fatigue Impact Scale (MFIS) (Kos et al. , 2005, Tellez et al. , 2005) is a 21-item self-report questionnaire measuring perceived fatigue impact with higher scores indicating greater impact. The Fatigue Assessment Instrument (FAI) (Schwartz et al. , 1993) is a 29-item self-report questionnaire measuring perceived fatigue severity with higher scores indicating greater severity . These scales, along with a single-item Visual Analogue Scale for fatigue (VAS) (Flachenecker, Kumpfel, 2002) in which current perceived fatigue is rated on a scale from 0 to 10, provided three measures of baseline fatigue. In our VAS, lower scores indicated greater fatigue. The Fatigue Severity Scale (FSS) (Flachenecker, Kumpfel, 2002, Krupp et al. , 1989) derived from 11 FAI items (Schwartz, Jandorf, 1993) and the MFIS were also used to classify fatigue at baseline.

The Conners Continuous Performance Test 3 (CCPT3); a standardised computerised assessment of attention (Conners, 2014) was administered before and after prolonged assessment, which served as

a measure of cognitive performance fatigability. Just prior to the administration of the second CCPT3, the VAS was re-administered to allow comparison with the previous VAS ratings, with the difference in scores providing a measure of perceived fatigue change. Each participant underwent an assessment of physical disability (EDSS) and completed a roughly 2.5 hour battery of clinically validated psychological and cognitive measures (Table 1). These assessments were delivered between the two administrations of the CCPT3 and VAS served as the intervention.

The data collection was completed over an eight month period by the same medical doctor (trained in EDSS assessments and the administration of the measures used), during single home visits. Measures were taken to remove distracting environmental elements, and the quietest room was used without other people present. Testing was undertaken at times most convenient for the participant and when they reported feeling their best and most alert. The order of administration was always the same (Figure 1), and all but the CCPT3 were pen-and-paper tasks.

Figure 1. Administration procedure for all measures.



Psychological measures included scales of anxiety, depression, sleep, coping, pain, and self-efficacy (Table 1). The cognitive battery comprised tests for estimating intelligence, attention, learning, memory, information processing speed, motor speed, and executive functioning.

Table 1. Measures administered in between the CCPT3 sustained attention tasks. *The VAS was administered twice alongside the CCPT3*

Physical	**Fatigue**	**Psychological**	**Cognitive**
EDSS	Modified Fatigue Impact Scale (MFIS)	Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983)	Wechsler Test of Adult Reading (Wechsler, 2001)
	Fatigue Assessment Instrument (FAI)	Medical Outcomes Survey Sleep Scale (Hays and Stewart, 1992)	Digit Span - Wechsler Memory Scale III (Wechsler, 1997)
	Visual Analogue Fatigue Scale [VAS]	Coping Inventory for Stressful Situations (Endler and Parker, 1994, 1999)	BIRT Memory & Information Processing Battery (Coughlan et al. , 2007)
		Pain Worksheet-Chronic Pain Coping Inventory (Jensen et al. , 2008)	Delis-Kaplan Executive Function System Letter & Category Fluency Trail Making Color-Word Interference (Delis et al. , 2001)
		General Self-Efficacy Scale (Schwarzer and Jerusalem, 1995)	Alternate Uses Test (Dippo, 2013)

Statistical analyses

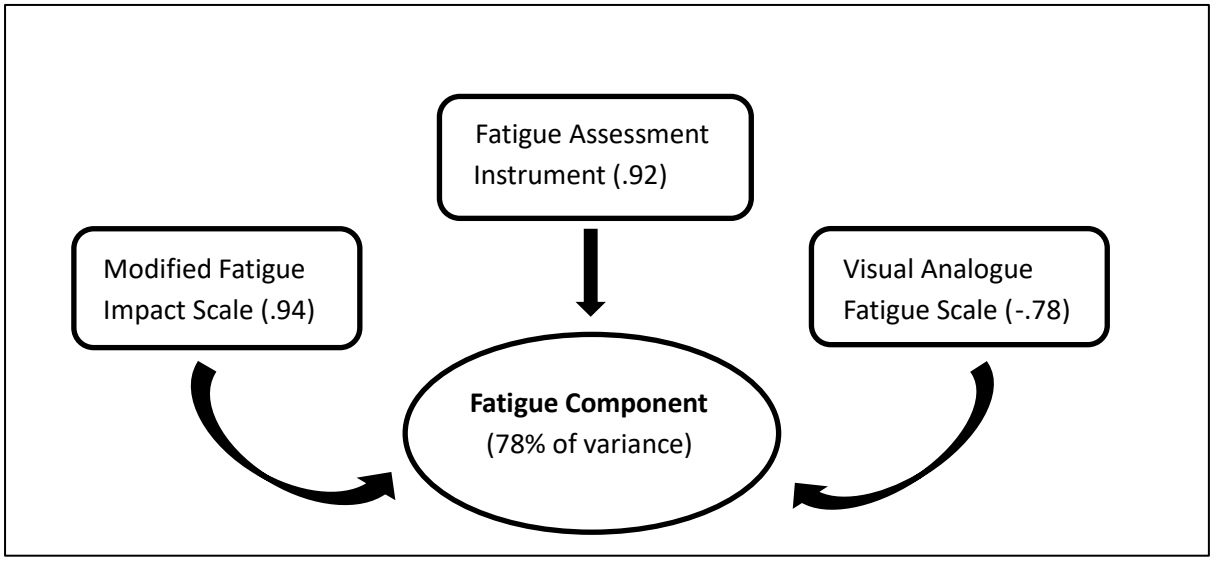
We used published cut-offs for the MFIS (Flachenecker, Kumpfel, 2002) and the 11-item FSS (Schwartz, Jandorf, 1993, Tellez, Rio, 2005) to classify perceived fatigue at baseline and published 'minimally important differences' (MID) (Khanna et al. , 2008, Nordin et al. , 2016) in pre- and post-intervention VAS scores to classify perceived fatigue change. The different MID in fatigue reported by Khanna and colleagues (Khanna, Pope, 2008) had a mean of 0.9 for improvement (range 0.82-1.12) and 1.2 for worsening (range 1.13-1.26) on a scale from 0 to 10. Therefore, we used differences of 1 or greater for improvement and 2 or greater for worsening as responses were indicated in whole numbers. Participants whose perceived fatigue improved were grouped with those who remained stable, due to the small numbers. Performance change was determined by reliable change in CCPT3

scores pre- and post-intervention. The CCPT3 Reliable Change Index formula (Conners, 2014) used standard error of difference to compute critical values.

Group differences across classifications of perceived fatigue, perceived fatigue change, and performance change were examined for demographic, clinical, cognitive, psychological, and fatigue variables using independent samples t-tests and one-way between-groups analyses of covariance. All cognitive scores were converted to standard scores. We used the Chi Square Test for Independence with Yates Continuity Correction to examine differences across these classifications with gender as well as cognitive impairment status. We classified participants as cognitively impaired if two or more cognitive scores were at or below the 5th percentile compared to test normative samples.

Using linear regression (method= enter) to predict baseline perceived fatigue, the three fatigue scales (MFIS, FAI, and VAS) used at the beginning of testing were reduced into a single fatigue factor using Principal Component Analysis (Figure 2).

Figure 2. Principal component analysis showing the principal fatigue component (factor loadings shown in parentheses)



Inclusion of independent variables was informed by recommendations that these demonstrate bivariate correlations above .30 with the dependent variable, and less than .70 with each other (Pallant, 2013). Anxiety, depression, sleep, pain, coping (emotion-focussed), self-efficacy, and EDSS were entered into the model with the perceived fatigue component as the dependent variable. Age, gender, disease duration, number of relapses, coping (task focussed and avoidance) and cognitive variables were excluded due to insufficient correlation.

Regression analysis was not used for perceived fatigue change (difference between pre- and post-testing VAS scores) as this did not correlate with the fatigue component or our other variables. Measures of performance change (differences between the first and second scores across nine CCPT3 variables) showed insufficient correlations with most fatigue (fatigue component and pre-or post-intervention VAS scores), demographic, clinical, and psychological variables. The correlations meeting our criteria for linear regression were within the CCPT3 perseveration change and reaction time change variables (mean response speed and consistency of response speed). Estimated intelligence and self-efficacy were entered into a model with perseveration change as the dependent variable. Letter fluency, Color-Word Interference (CWIT) Condition 3 (interference trial), number of impaired cognitive scores, and estimated intelligence were entered into a model with mean response speed change as the dependent variable. Post-intervention fatigue (2nd VAS), estimated intelligence, visual learning, CWIT Condition 3, number of impaired cognitive scores, and avoidant coping were entered into the final model with response speed consistency change as the dependent variable. The analyses were completed using IBM SPSS Statistics 25 and the significance level adopted $p<0.05$.

Results

Sample characteristics

A total of 304 potential participants were identified from the database. Of these 120 met the study criteria and were invited to take part in the study. 62 participants responded and were recruited into

the study (table 2 shows demographic details). One participant's testing was discontinued due to difficulty completing the tasks. A total of 61 participants were included in the final dataset.

Table 2. Demographic and clinical features of the sample

N	61
Age in Years (mean [SD])	42.5 [11.3]
Gender (Female : Male)	45: 16
Estimated Intelligence (mean[SD]) Test score mean 100 (SD 15)	109.3 [6.4]
HADS Anxiety (mean [SD]) Depression (mean [SD])	6.9 [4.6] 4.2 [3.7]
EDSS (median)	2.5
Duration from Disease Onset (mean) **Duration from Diagnosis** (mean)	10 years 5 years
Relapsing Remitting **Secondary Progressive** **Primary Progressive**	47 9 5

Baseline Fatigue

Roughly half of participants were fatigued at baseline using the MFIS or FSS with 39% (24 participants) classified as fatigued by both scales (Table 3).

Table 3. Fatigue classifications

	MFIS (cut off 38)	**FSS (cut off 5)**	**Classification agreement**
Fatigued	n=30 – 49%	n=28 – 46%	n=24 – 39%
Not fatigued	n=31 – 51%	n=33 – 54%	n=27 – 44%

Those classified as fatigued using the MFIS had greater fatigue on the baseline VAS; more anxiety and depression; poorer sleep quality; greater pain; more emotion-focussed coping; less self-efficacy; more disability (higher EDSS); and greater response variability on the first CCPT3 than those not fatigued (Table 4). There was no association between MFIS classification and cognitive impairment status or gender.

Table 4. Comparison of those classified as fatigued or not fatigued using the MFIS

MFIS fatigued vs not fatigued Mean(SD)				
Variable	**Fatigued n=30**	**Not fatigued n=31**	**t - score**	**p - value**
Baseline VAS*	5.8 (1.7)	7.4 (2.4)	2.96	0.005
Anxiety	9.6 (4.3)	4.3 (3.1)	-5.415	<0.0005
Depression	6.9 (3.5)	1.7 (1.7)	-7.165	<0.0005
Sleep quality	42.1 (8.2)	47.2 (7.8)	2.498	0.015
Pain	2.1 (1.9)	0.7 (1.8)	-2.785	0.007
Emotion-focussed coping	52.9 (10.8)	41.6 (8.9)	-4.445	<0.0005
Self-efficacy	28.9 (6.0)	33.6 (4.4)	3.445	0.001
Disability (EDSS)	3.7 (2.2)	2.2 (2.0)	-2.742	0.008
Response variability (CCPT3)	51.1 (7.2)	46.7 (5.7)	-2.637	0.011

* Lower VAS scores indicate greater fatigue whereas higher scores on other variables indicate more of the variable.

The effect of MFIS classification on depression scores remained significant (F=12.323, p=.001) after the other variables demonstrating significant differences were controlled for. However, when adjusting for depression, only the differences in anxiety and emotion-focussed coping remained (F=5.09, p=.028 and F=16.507, p<.0005, respectively).

Those fatigued using the FSS had greater fatigue on the baseline VAS; more anxiety and depression; greater pain; more emotion-focussed coping; less self-efficacy; higher EDSS; and greater slowing of reaction times on the first CCPT3 than those not fatigued (Table 5). There was no association between FSS classification and cognitive impairment status or gender.

Table 5. Comparison of those classified as fatigued or not fatigued using the FSS

FSS fatigued vs not fatigued mean (SD)				
Variable	**Fatigued n=28**	**Not fatigued n=33**	**t - score**	**p - value**
Baseline VAS*	5.6 (1.4)	7.6 (2.4)	3.92	<0.0005
Anxiety	9.1 (3.9)	5.0 (4.3)	-3.783	<0.0005
Depression	6.5 (3.5)	2.3 (2.8)	-5.098	<0.0005
Pain	2.0 (1.9)	0.9 (1.9)	-2.123	0.038
Emotion-focussed coping	51.3 (11.6)	43.6 (9.9)	-2.803	0.007
Self-efficacy	29.5 (6.1)	32.8 (4.9)	2.301	0.025
Disability (EDSS)	3.7 (1.9)	2.3 (2.3)	-2.427	0.018
Reaction time (CCPT3)	55.0 (10.8)	49.3 (7.7)	-2.377	0.021

*Lower VAS scores indicate greater fatigue whereas higher scores on other variables indicate more of the variable. Higher scores on reaction time indicate greater slowing of reaction times.

The effect of FSS classification on depression scores remained significant (F=6.422, p=.014) when the other variables demonstrating significant differences were controlled for. However, after adjusting for depression, only the difference in emotion-focussed coping remained (F=4.066, p=.048).

For cognition, the group comparisons using the MFIS and FSS cut-offs yielded a single difference (delayed visual recall, t=2.333, p=.023) with the former, and two differences (information processing, t=2.222, p=.03; motor speed, t=2.056, p=.044) with the latter scale. These effects disappeared with depression as a covariate. There were no differences in the number of impaired cognitive scores across classifications of either scale.

The linear regression model with the perceived fatigue component as the dependent variable was significant (F=10.881, p<.0005) with 53.5% of the variance in perceived fatigue explained by the model (Adjusted R Square .535). Depression, sleep quality, and emotion-focussed coping made significant contributions to the variance in perceived fatigue (Table 6). With shared variance partialled out, the unique proportions of variance accounted for by these variables were 4.5%, 4.6%, and 4.9%, respectively.

Table 6. Regression model output with the fatigue component as the dependent variable

Model	Beta	p - value	Part correlation
Anxiety	-.055	.697	-.034
Depression	.331	.019	.213
Sleep quality	-.238	.017	-.216
Pain	.147	.137	.133
Emotion-focussed coping	.288	.014	.223
Self-efficacy	-.099	.341	-.084
Disability (EDSS)	.170	.108	.144

Fatigue Change

Comparing pre- and post-intervention VAS scores, 35 (57.4%) rated their fatigue worse after intervention, 15 (24.6%) rated their fatigue the same, and 11 (18%) rated their fatigue as improved.

Those fatigued at baseline (MFIS or FSS) demonstrated greater post-intervention fatigue (t=2.524, p=.014 and t=3.807, p<.0005, respectively) than those not fatigued.

The effect of MFIS classification on post-intervention perceived fatigue disappeared when the variables demonstrating significant group differences at baseline were controlled for. The pre-intervention VAS alone accounted for a significant proportion of variance (37.6%) in post-intervention VAS fatigue (F=29.566, p<.0005). Similarly, the effect of FSS classification on post-intervention fatigue disappeared when the variables differing at baseline were controlled for. Unsurprisingly, pre-intervention VAS alone accounted for significant variance (35.5%) in post-intervention fatigue (VAS) (F=28.115, p<.0005).

Classification according to MID in perceived fatigue resulted in fatigue worsening in 24 (39.3%) and either stable or improved fatigue in 37 (60.6%). Those whose fatigue worsened demonstrated more anxiety (t=-2.417, p=.021), depression (t=-2.471, p=.016) and less self-efficacy (t=2.127, p=.038), with no other differences across our variables. Depression means across groups were 'normal' (5.7 vs 3.3). The anxiety mean for those who worsened was 'mild' (8.7), and 'normal' for those who remained stable or improved (5.7).

There were no associations between the baseline perceived fatigue classifications and fatigue change status (using MID). Similarly, there was no association between MID classification and gender, with 25% of males (n=4) and 44% of females (n=20) demonstrating worsened fatigue. However, grouping the raw fatigue change scores into 'improved (or stable)' and 'worsened' was associated (X^2 =4.69, p=.03) with gender, with 31% of males (n=5) and 67% of females (n=30) demonstrating worsened fatigue. There were no gender differences in psychological variables, baseline fatigue measures, or post-intervention fatigue, but fatigue change (t=-2.054, p=.044) differed. Females demonstrated more worsening than males, but this difference was no longer significant once depression, anxiety and self-efficacy were accounted for.

Cognitively, those whose fatigue worsening was greater than the MID demonstrated more reliably changed CCPT3 scores (Table7); greater worsening in reaction times and response speed variability; weaker visual learning, information processing speed, and category fluency; as well as slower performance during the divided attention (Trail Making Condition 4) and inhibition tasks (CWIT Condition 3).

Table 7. Comparison of those whose fatigue worsened or remained stable based on MID

Fatigue worsened vs remained stable mean (SD)				
Variable	**Worsened n=24**	**Stable n=37**	**t - score**	**p - value**
Number of reliably changed CCPT3 scores	1.8 (1.5)	0.6 (0.9)	-3.430	0.002
Reaction time (CCPT3) change	-4.1 (8.8)	0.08 (4.4)	2.173	0.038
Response variability (CCPT3) change	-5.5 (10.0)	1.1 (6.6)	3.108	0.003
Visual learning (z-score)	-0.4 (1.1)	0.1 (0.9)	2.106	0.039
Information processing speed (z-score)	-0.7 (1.0)	-0.2 (1.0)	2.042	0.046
Category fluency (scaled score)	9.5 (3.4)	12.0 (3.1)	2.963	0.004
Trail Making Condition 4 (scaled score)	7.8 (3.7)	10.1 (3.2)	2.463	0.017
CWIT Condition 3 (scaled score)	7.8 (4.3)	10.7 (2.6)	2.833	0.008

* z-scores have a mean of 0 and standard deviation of 1 whereas scaled scores have a mean of 10 and standard deviation of 3.

After adjusting for estimated intelligence and the psychological variables that differed between groups, only the differences in number of reliably changed CCPT3 scores (F=8.096, p=.006) and response speed variability change (F=5.441, p=.023) remained. There was no association between MID classification and cognitive impairment status.

When comparing the cognitively impaired (n=25, 41%) to those unimpaired, there were no differences in baseline fatigue variables, fatigue change or post-intervention fatigue. Whilst there were differences across cognitive variables, the number of reliably changed CCPT3 scores did not differ. There was a difference in EDSS scores (t=-3.979, p<.0005), with the impaired group demonstrating higher EDSS scores (mean [SD]= 4.3[2.2] versus 2.1[1.9]). The group effect remained significant (F=10.941, p=.002) accounting for 16.8% of the variance in EDSS scores with fatigue variables, depression, and age as covariates.

Performance Fatigability

We found 34 (55.7%) of our sample demonstrated reliable performance change on one or more CCPT3 variables (mean=1.9, range 1-5) and 27 (44.3%) did not. Baseline fatigue variables did not differ between groups, but those with reliable change had more anxiety (t=-2.058, p=.044), greater fatigue change (t=-2.866, p=.006) and more post-intervention fatigue (t=3.056, p=.003). There was an association between fatigue change status based on MID and CCPT3 reliable change status (X^2=10.44, p=.001) with 38% of those whose fatigue remained stable or improved and 83% of those whose fatigue worsened demonstrating reliable change.

There were no differences on the baseline CCPT3, in estimated intelligence, or in the number of impaired cognitive scores. Whilst the reliable change group had slower motor speed (t=2.222, p=.03) and performance speed on the inhibition task (t=2.564, p=.013), there were no other cognitive differences. There were no differences in age, disease variables, EDSS, depression, sleep, pain, coping, or self-efficacy.

There was a significant association (X^2=4.01, p=.045) between reliable change status and gender, with 31% of males and 64% of females demonstrating reliable CCPT3 change. Females had significantly more reliably changed CCPT3 scores than males (t=-2.123, p=.038), but they did not differ on initial CCPT3 scores. There was no association between gender and cognitive impairment status, and where the genders differed on cognitive variables (verbal learning, t=-3.39, p=.001; information processing speed, t=-2.712, p=.009; and motor speed, t=-2.379, p=.021) females outperformed males. Males had longer disease duration (t=2.111, p=.048), but EDSS did not differ across genders.

Predictors of performance fatigability

The linear regression model with perseveration change as the dependent variable was significant (F=10.488, p<.0005) explaining 24% of the variance in perseveration change (Adjusted R Square .24).

Both estimated intelligence and self-efficacy made unique contributions to the model with little shared variance; 14% and 10.5% respectively (Table 8).

Table 8. Regression model output with perseveration change as the dependent variable

Model	Beta	p – value	Part correlation
Estimated intelligence	.377	.001	.376
Self-efficacy	-.326	.005	-.325

The second model with reaction time change as the dependent variable was significant (F=6.628, p<.0005) explaining 27.3% of the variance (Adjusted R Square .273). Estimated intelligence was the only independent variable to make a unique contribution, which was 5.5% of variance in reaction time change scores with shared variance partialled out (Table 9).

Table 9. Regression model output with reaction time change as the dependent variable

Model	Beta	p - value	Part correlation
Estimated intelligence	.295	.037	.235
Letter fluency	.083	.548	.067
CWIT Condition 3	.002	.990	.001
Number of impaired cognitive scores	-.291	.088	-.191

The last model with response speed consistency change as the dependent variable was also significant (F=4.250, p=.001) accounting for 24.5% of the variance in scores (Adjusted R Square .245). Post-intervention fatigue was the only independent variable to make a unique contribution, accounting for 8% of variance in response speed consistency change scores with shared variance partialled out (Table 10).

Table 10. Regression model output with response speed consistency change as the dependent variable

Model	Beta	p - value	Part correlation
Estimated intelligence	.224	.141	.168
CWIT Condition 3	-.079	.642	-.052
Number of impaired cognitive scores	-.231	.200	-.145
Post-intervention fatigue (2nd VAS)	.300	.014	.283
Avoidant coping	.189	.128	.174
Visual learning	.010	.945	.008

Discussion

We combined a computerised measure of cognitive performance fatigability with a multifactorial approach to fatigue assessment to highlight different factors in perceived fatigue and performance fatigability. In keeping with previous studies, we highlight that fatigue was not a unitary construct, and appeared more closely related to indirect than direct factors (Kos, Kerckhofs, 2008, Strober and Arnett, 2005).

The links between mood, sleep and fatigue have been previously established (Chinnadurai et al. , 2018, Strober and Arnett, 2005, Veauthier and Paul, 2014), and coping has been recognised as an important mediator between MS (including fatigue) and wellbeing (Grech et al. , 2016). However, our results suggest emotion-focussed coping has a direct influence on perceived fatigue. Whilst coping can predict depression in MS (Brown et al. , 2009), construct overlap cannot sufficiently explain our findings. We highlighted that whilst depression, sleep and coping may interrelate, they account for distinct contributions in perceived fatigue.

Perceived fatigue change and cognitive performance change

Those whose perceived fatigue worsened demonstrated more anxiety, depression, and less self-efficacy than those whose fatigue remained stable or improved. Perceived fatigue change appeared to show little association with baseline fatigue, cognitive impairment, physical disability, or other demographic and clinical variables. Our results suggest a role for indirect factors not only in perceived baseline fatigue, but also in fatigue change. This raises the question of whether the associations between fatigue change and reliable performance change and worsened performance variability could be seen as in keeping with the possible effects of psychological variables on cognition (Brose et al. , 2010, Rock et al. , 2014, Vytal et al. , 2012).

Without any differences in perceived baseline fatigue, those who demonstrated reliable performance change had more anxiety, fatigue change, and post-intervention fatigue. However, only one fatigue

variable (post-intervention fatigue) predicted a single CCPT3 change variable. Therefore, whilst perceived fatigue change and reliable performance change may co-occur, it is not clear to what degree change in these is driven by fatigue per se. Contrary to other studies demonstrating relationships between perceived fatigue and cognitive performance fatigability (Cehelyk, Harvey, 2018, Wolkorte, Heersema, 2015) or motor fatigability (Loy, Taylor, 2017, Skurvydas, Brazaitis, 2011, Zijdewind, Prak, 2016), our results provide little general support for the role of fatigue variables in performance change. Whilst there was a link between cognitive impairment status and EDSS, neither had influence on perceived fatigue, fatigue change, or performance change, which are results that diverge from some other studies (Biberacher, Schmidt, 2018, Ghajarzadeh, Jalilian, 2013).

Gender and fatigue

Unexpectedly, we found that females demonstrated more worsening of fatigue and cognitive performance compared to males. However, once anxiety, depression and self-efficacy were adjusted for, the gender difference in fatigue change was attenuated. These results contrast somewhat from studies suggesting fatigue in MS being gender invariant (Bakshi, 2003, Flachenecker, Kumpfel, 2002) and gender having little influence on the prevalence of cognitive fatigue (Sander et al. , 2016) or on performance fatigability (Skurvydas, Brazaitis, 2011, Wolkorte, Heersema, 2015).

Limitations

A limitation of this study is that we did not use a group of healthy controls. However, the validity of our results is supported by research into MID in fatigue (Khanna, Pope, 2008, Nordin, Taft, 2016) and reliable performance change on the CCPT3. As part of the standardisation procedures this test was normed on 600 healthy adults (of which 384 covered the age range of our sample) with test-retest reliability measured on 63 adults with a mean age (43.5), similar to that of our sample. These norms may indeed enable more robust measurement of impairment and reliable change than using a small control group more vulnerable to sampling effects.

We note the generally low EDSS scores in our sample and recognise there may be greater fatigue variability or impact with higher EDSS scores. However, these lower EDSS scores were not necessarily without meaning, considering the link between these and cognitive impairment in our study. These results are in keeping with recent research highlighting cognitive impairment even in low EDSS 'benign' MS patients (Tallantyre et al. , 2018). We also acknowledge that we did not differentiate between MS subtypes (majority relapsing remitting), which might make the results less generalisable for patients with progressive disease. Lastly, as we preferred to test participants in their own homes, we recognise that the different testing environments may have introduced some variability to performances that would be minimised in a controlled testing environment. However, we hope that any variance from different environments might be offset by our preference to optimise participant comfort and engagement.

Concluding remarks

Our results suggest perceived fatigue (and even sustained cognitive performance to a degree) has the potential to be influenced by interventions for psychological variables such as depression, anxiety, coping, and self-efficacy. Interestingly, prolonged cognitive effort appeared to improve fatigue in 18% of our sample, suggesting a possible role for cognitive stimulation in improving perceived fatigue. Providing targeted treatments for fatigue have the potential to effectively enhance both psychological wellbeing and quality of life, with the value especially of non-pharmacological interventions for fatigue already demonstrated (Miller and Soundy, 2017, Penner and Paul, 2017, van den Akker et al. , 2016).

There has been a drive to instigate multifactorial assessment and treatment of fatigue in MS (Braley and Chervin, 2010). In keeping with this, our results suggest we need to acknowledge multiple influences not only in examining perceived fatigue, but also when measuring cognitive performance fatigability. We hope that our study will contribute to understanding fatigue in MS and to furthering treatment options.

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