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Article in Topics in Stroke Rehabilitation · June 2016
Impact Factor: 1.45 · DOI: 10.1080/10749357.2016.1188475

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To cite this article: Trine Schow, Thomas William Teasdale, Kirsten Jensen Quas & Morten Arendt Rasmussen (2016): Problems with balance and binocular visual dysfunction are associated with post-stroke fatigue, Topics in Stroke Rehabilitation, DOI: 10.1080/10749357.2016.1188475

To link to this article: http://dx.doi.org/10.1080/10749357.2016.1188475

Published online: 07 Jun 2016.

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Problems with balance and binocular visual dysfunction are associated with post-stroke fatigue

Trine Schow1, Thomas William Teasdale2, Kirsten Jensen Quas1, Morten Arendt Rasmussen3,4

1Brain Injury Center – BOMI, Roskilde, Denmark, 2Department of Psychology, University of Copenhagen, Copenhagen, Denmark, 3Faculty of Science, Spectroscopy and Chemometrics University of Copenhagen, Frederiksberg, Denmark, 4Danish Paediatric Asthma Centre, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

Background: Fatigue after stroke is hard to define and measure and how it is associated with other complications after stroke still needs to be explored. These issues are relevant in stroke rehabilitation and in the patient’s daily life.

Objective: To investigate fatigue after stroke and its relation to balance, gait, and Binocular Visual Dysfunction (BVD).

Methods: Adults with stroke (n=29, age 18–67 years) were tested with the Modified Fatigue Impact Scale (MFIS), objective and subjective BVD measures, Balance Evaluation Systems Test, Ten Meter Walk Test, and a Health-Related Quality of Life questionnaire, before and after a four-month intervention program and at three- and six-month follow-ups. We used principle component analysis to extract underlying factors of MFIS. Associations between MFIS factors and patient characteristics were analyzed by repeated measures ANOVA. The associations between MFIS factors and physical measures were assessed using pairwise correlations.

Results: Three components were extracted from the MFIS, explaining 71% of variance: Cognitive fatigue, Physical fatigue and Arousal. We found that women register higher MFIS scores than men. There was a strong association between the level of Cognitive and Physical Fatigue and BVD, between Arousal and balance and dizziness, and between Cognitive Fatigue and gait.

Conclusion: The three extracted components of MFIS proved clinically informative. The arousal component revealed particularly interesting results in studying fatigue. The correlation analysis shown at this component differs from cognitive and physical fatigue and describes another aspect of PSF, important in future treatment and research.

Keywords: Fatigue, Multivariate analysis, Stroke

Fatigue is a common problem after stroke and is associated with several disabilities. The prevalence of post-stroke fatigue (PSF) is reported as varying between 70% at one month post-stroke, 64–68% after six months, and 74% after one year. Several studies have reported on PSF, but no universally accepted definition or standard measure has been agreed upon. Lerdal et al. suggested a subjective definition of PSF used in the field of multiple sclerosis, namely “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.” The lack of definition and “gold standard” measurements cause difficulties in comparing results from different studies and hence hampers the development of effective treatment strategies. PSF appears to be a multidimensional construct, most often measured by subjective self-reporting generic rating scales as no rating scale has, until very recently, been developed specifically to measure fatigue after stroke. The current scales used to measure PSF are more generic scales that may not capture PSF adequately, and other scales have a specific focus on e.g. only mental fatigue: Examples of generic scales are: The Multidimensional Assessment of Fatigue originally developed for people with rheumatoid arthritis, The Fatigue Severity Scale was developed by Krupp et al. for patients with multiple sclerosis and other autoimmune disease, the Checklist Individual Strength (CIS) developed for patients with chronic fatigue syndrome and the PROMIS® Fatigue Item Bank to be used for all patient groups. An example of a more specific scale are: The Mental fatigue scale developed for patients with stroke, but focus only on the mental fatigue where the Brief Fatigue Inventory and the Fatigue Assessment Scale suffer from feasibility problems. Remedying the situation, Visser-Keizer
et al.\textsuperscript{13} have published a subjective rating scale specific to measuring the impact of PSF, this being the first of its kind published after the present study was initiated.

Several factors such as age, gender, living conditions, stroke characteristics, pre-stroke fatigue, anxiety and depression have all been found to be associated with PSF. However, there are conflicting results among different studies.\textsuperscript{4} A few studies have focused on physical factors and have found an association between PSF and higher energy expenditure.\textsuperscript{15} In a recent review, Nadarajah and Goh\textsuperscript{16} suggest that PSF assessment should include a measurement instrument that covers physical, mental, and psychological fatigue and involving an evaluation of both the severity and the impact of fatigue.

In our rehabilitation center we treat patients who suffer from a combination of binocular visual dysfunction (BVD) and balance problems. These patients often report problems with PSF when experiencing difficulties conducting visual near-work activities such as reading and watching TV. They also have problems with activities that demand postural stability in standing and moving positions, due to their balance impairment.\textsuperscript{14} We did not find any studies reporting an association between BVD and fatigue, but a few other studies have investigated the association between physical performance and PSF. Miller et al.\textsuperscript{17} and Michael et al.\textsuperscript{15} found an association between balance and PSF, whereas a study by Hoang et al. found no such association.\textsuperscript{18}

The objective of the present study has been to examine the validity of the MFIS in a population of people with stroke, and to investigate whether there is an association between fatigue and problems of binocular visual dysfunction (BVD) and balance and gait and quality of life.

\textbf{Method}

We have conducted a pre- and post-intervention study, including follow-up data. The project has been approved by the Danish Data Protection Agency j.nr. 2014-41-3324. Participants were recruited from 22 different municipalities and three regional hospitals. Thirty subjects fulfilled the inclusion criteria. At the end of the study, one was hospitalized with depression, such 29 subjects were enrolled. Details of the study, recruitment method, outcome measures, and more are described elsewhere.\textsuperscript{19}

\textbf{Inclusion criteria}

Subjects with stroke within 3–36 months prior to entry into the program and with balance and BVD problems. Age 18–67 years.

\textbf{Exclusion criteria}

Previous history of BVD and balance problems, hemianopsia and any other BVD, progressive and/or severe eye disease, progressive brain damage, and/or severe cognitive problems hindering group training; any psychiatric diagnosis or drug abuse.

\textbf{Outcome measures}

\textbf{Baseline clinical characteristics}

Gender, age, type of stroke (hemorrhagic/ischemic stroke), location of the lesion (left, right, brain stem, cerebellar injury or diffuse), and time since injury.

\textbf{Subjective measures}

Fatigue was measured using the Modified Fatigue Impact Scale (MFIS) which has recently been validated in a brain injury population.\textsuperscript{20} Participants rated how often fatigue has affected 21 functions during the preceding 4 weeks using a scale from 0 (never) to 4 (almost always). The sum of these ratings thus ranges from 0 to 84 with higher values indicating greater impact of fatigue. The original published guidelines for use with patients having multiple sclerosis specify that the items can be aggregated into a total score (21 items) as well as three subscales: Physical (9 items), Cognitive (10 items), and Psychosocial (2 items), while a recently published paper on brain injury patients found only two subscales, Physical (10 items) and Cognitive (11 items).\textsuperscript{20}

Health-Related Quality of Life (HRQoL) was assessed using the The EuroQol five dimension three-level measure (EQ-5D-3L).\textsuperscript{21} This is a generic health-related quality of life questionnaire that consists of two parts. Part one covers health status in five dimensions and part two, used in this study, is a 200 mm Visual Analog Scale (VAS) rating state of health, between 0 (worst possible) and 100 (best possible).

The BVD burden was assessed by the Vertical Heterophoria Symptom Questionnaire (VHS-Q). This is a self-administrative survey used to assess improvement of symptoms for vertical heterophoria (VH).\textsuperscript{22} It comprises 25 items, each with a score 0–3. The higher the score, the more severe the problems (a validation of VHS-Q is in progress).

\textbf{Objective BVD test}

Stereo acuity At Near (SAN) was assessed using the Randot Stereotest (Stereo Optical Co, Chicago, IL)\textsuperscript{23} with subjects wearing Polaroid spectacles. The test stereogram was held at a distance of 40 cm from the subject during testing. Participants with refractive errors wore their spectacles under the Polaroid lenses. Participants were asked to determine which circle in each successive group appeared to “pop out of the page.” This procedure was repeated until two mistakes were made successively. Threshold stereo-acuity level was recorded in seconds of arc.
Reading-related saccadic eye movements were measured using the King–Devick test (K-D). This test involves reading aloud a series of randomized single numbers from left to right as quickly as possible. Scoring for the K-D is based on time taken to read 40 numbers aloud.

Near Point of Convergence (NPC) was assessed using a Wolff Wand placed along the subject’s visual midline. Then the Wand was slowly moved towards the bridge of the nose. Break of NPC was recorded either when the patient reported diplopia or the examiner observed one eye turning away. \(^{24}\)

Binocular fusion was tested using the Keystone Telebinocular. The Keystone Visual Skills Tests are measurements of habitual responses. All results are taken under equal excitation to accommodation and convergence. To measure binocular fusion, the Keystone Visual Skills test cards at both distance (BFD) (the DB-4 K) and near-point distance (BFN) (DB-5 K) were used and ability to reach binocular fusion were recorded as yes or no. \(^{24}\)

**Balance and gait**

Balance was assessed by the Balance Evaluation Systems Test (BESTest). \(^{26}\) The BESTest is based on a conceptual model of balance control investigating six systems of postural control: Biomechanical, Stability Limits, Postural Responses, Anticipatory Postural Adjustments, Sensory Orientation, and Dynamic Balance during Gait. Each system involves 5–7 tasks, scored on a rating scale from 0 to 3 (there are a 36 task in total). The total maximum score is 108 points, this being the sum of all of the individual items. The raw scores are converted into percentages; higher scores indicate better balance performance.

Gait performance was assessed by Ten Meter Walk Test (10MWT). \(^{27}\) We studied gait speed at comfortable and safe maximum walking speed using a standard approach to assess gait performance. \(^{27}\)

Subjects were tested with the total test battery at baseline, at the end of training and at three- and six-month follow-ups.

**Statistical analysis**

**Extraction of factors from MFIS data**

Principle component analysis (PCA) with varimax rotation was used with the MFIS in order to identify underlying constructs related to different kinds of fatigue. The number of factors retained in the model was determined from a screen plot of eigenvalues and the interpretability of the rotated factor loadings, and was further validated by a non-parametric bootstrap procedure (with 10,000 iterations), determining the factor loading uncertainty. We evaluated the sensitivity of the factors by varying the number of components from three to five. In addition to these data-derived factors, a total score (the sum of all 21 questions) was calculated. This additional factor is not independent of the data-derived PCA factors and is merely a more global representation of the MFIS data.

Pairwise correlation between the MFIS constructs and the subjective and objective visual measures and balance and gait and HRQoL were analyzed and visually presented using heat maps. In this association analysis, we also included the MFIS two-factor model by Schieser et al., \(^{20}\) namely MFIS-cognitive and MFIS-physical, to establish whether our MFIS factor model added revealing information.

All statistical analyses were conducted in Matlab® R2014b using the PLStoolbox (ver 7.9.5 — Eigenvector Inc \(^{3}\)), the statistical toolbox v 8.1 and *in-house* algorithms for bootstrapping and plotting.

**Results**

Patient demographic characteristics are shown in Table 1. We used a PCA with varimax rotation to identify subscales from the MFIS 21 questions and to examine whether they structured according to the two subscales recently found in TBI patients. \(^{26}\) Based on the eigenvalue and interpretability of the factor loadings, three components were extracted, explaining 67% of variance (see Fig. 1). These three components were identified as (1) “Cognitive” including nine questions and explaining 28.9% of the variance, (2) “physical” including six questions, explaining 22.1% and (3) “arousal” including six questions and explaining 15.9% of the variance. The bootstrap analysis showed high internal consistency for all three components (Fig. 2). Sensitivity analysis revealed consistency in the factor structure of the three components, which were practically similar for models with three to five components. Question 14, regarding physical uncomfortable/body, was found associated with both physical fatigue (component 2) and arousal (component 3). In this regard, it associates with two distinct patterns that intuitively both results in discomfort, however, the strongest association were observed for component 2 (physical fatigue).

Table 2 shows the relationships between the MFIS components and the patient background variables. The strongest predictor of PSF is time in the treatment
Problems with balance and binocular visual dysfunction are associated with post-stroke fatigue.

Female gender is associated with higher level of cognitive fatigue (component 1) and more problems with arousal/mobilization of energy (component 3) and the middle-aged group (age 48–55 years) has likewise a higher level of cognitive fatigue. There was also an association of brain stem injury and cognitive fatigue.
There is in general a very strong association between the MFIS total and BVD measures (except from stereopsis (SAN) and VHSQ Vision). VHSQ Dizziness was, interestingly, very strongly associated with arousal (component three MFIS) and not with the new physical fatigue (component 2), but strongly associated with the old physical fatigue. It seems that the association between fatigue and dizziness is driven by arousal/ the ability to mobilize energy more than physical fatigue. Arousal was also associated with reading problems defined by K-D. VHSQ Pain/sensation was associated with all components of fatigue. Cognitive fatigue was very strongly associated with reading problems (VHSQ reading and K-D) and physical fatigue was related to visual problems in terms of K-D and near point convergence (NPC) and binocular fusion (BFN).

We found a disparity between our factor structure and the TBI MFIS structure. Our arousal component was mainly associated with dizziness, pain and K-D and the new physical fatigue scale strongly associated to vision in terms of VHSQ pain/sensation, VHSQ vision, BFN, convergence (NPC), and K-D, whereas the TBI-MFIS-phys was associated with dizziness and pain and not VHSQ vision. Moreover, we found an association between HRQoL (EQ-VAS) and binocular coordination (BFN) and NPC (see Fig. 3).

Associations between MFIS and measures of balance and gait show that MFIS cognitive is related to walking speed and the BESTest domain reactive postural control. Arousal is also associated with reactive postural control and postural adjustments and stability in gait. Physical fatigue is, very interestingly, not associated with balance or walking speed (see Fig. 4) HRQoL was not related to balance and walking speed.

**Discussion**

This study found that the factor structure of the MFIS in a sample of stroke patients comprised three components, “Cognitive fatigue”, “Physical fatigue,” and “Arousal”. This is similar in number to the original scale, however, the three components are different in structure. The original “Psychosocial” component items were found to load on “arousal” in this study, and so did questions related to alertness and physical motivation/mobilization of energy. Our cognitive component consists of questions related to thinking, mental motivation and attention, and the physical component involved questions regarding clumsiness, physical activity, muscle weekness, and physical discomfort. At first, we also found a fourth component involving only one question regarding physically uncomfortable. However, in further analysis this component revealed less information on its own and since the question “uncomfortable” was associated with the component physical fatigue we retained a three-component model, which sufficiently describe the questionnaire data, without loss of systematic variation in relation to measures of fatigue.

The first TBI validation of the MFIS comprised just two components involving 106 veterans with mild or moderate TBI. In contrast to the study of MFIS in a TBI population, we found that coordination/clumsiness loaded as in the original scale on the physical fatigue dimension. An explanation of this difference could be that subjects binocular visual dysfunctions and balance problems may lead to them bumping into things and in that perspective be a physical thing per se in contrast to the TBI study, where clumsiness may occur due to cognitive problems. Thus, the difference in results between this study and ours could be the nature of the brain injury and following dysfunctions and the possible number of participants.

Notably, our PCA revealed a component of arousal. A more descriptive name could be “mobilisation of energy,” since this component includes a question on being motivated for anything physical, using energy, and leaving the house. Questions regarding physical fatigue are more related to muscle weakness, fatigability (fatigue after physical activity), and physical condition. When

**Table 2 Association between factor scores and patient characteristics**

<table>
<thead>
<tr>
<th>Component (cognitive)</th>
<th>Time</th>
<th>Injury localization</th>
<th>Injury localization × time</th>
<th>TSI</th>
<th>TSI × time</th>
<th>Age</th>
<th>Age × time</th>
<th>Home-work</th>
<th>Home-work × time</th>
<th>Sex</th>
<th>Sex × time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component 2 (physical)</td>
<td>&lt;0.001</td>
<td>0.57</td>
<td>0.88</td>
<td>0.73</td>
<td>0.29</td>
<td>0.67</td>
<td>0.20</td>
<td>0.84</td>
<td>0.27</td>
<td>0.95</td>
<td>0.59</td>
</tr>
<tr>
<td>Component 3 (arousal)</td>
<td>&lt;0.001</td>
<td>0.87</td>
<td>0.13</td>
<td>0.42</td>
<td>0.68</td>
<td>0.23</td>
<td>0.69</td>
<td>0.33</td>
<td>0.64</td>
<td>0.01</td>
<td>0.78</td>
</tr>
<tr>
<td>Total</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>0.37</td>
<td>0.01</td>
<td>0.01</td>
<td>0.03</td>
<td>0.56</td>
<td>0.86</td>
<td>0.48</td>
<td>0.28</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Note: All numbers are p-values; p-values >0.05 are in bold.
determining treatment, it seems important to be able to
distinguish between muscle weakness, poor physical con-
dition, and problems with alertness, motivation for being
active and do social things (arousal). This is a very differ-
ent aspect of fatigue, and require very different treatments
such as physical therapy, neuropsychological coaching,
cognitive therapy, and more, which the data also support,
showing the difference in associations with balance and
visual problems.

The only question separating our cognitive subscale
and the original one is that of clumsiness. However, this
small difference can explain why we did not find any
association between self-reported dizziness and cognitive
fatigue. Instead we found an association between arousal
and self-reported dizziness. Our association analysis
also showed that reading is related to cognitive fatigue.
Reading requires a lot of rapid information processing
and working memory. High levels of cognitive fatigue are
therefore very likely to result in problems with reading,
and vice versa. All our participants suffered from reading
problems, due to BVD and therefore reading might con-
ssume extra amount of cognitive energy.

Interestingly, the BESTest total score correlated with
arousal but not with physical fatigue. It seems plausible
that there is a correlation between arousal and balance
(involving postural adjustment and reactive postural
control), since this domain demands the mobilization of
energy. Postural adjustment and reactive postural control
are necessary in many daily life activities such as walking,
cycling, standing in a bus or train, and being pushed in a
crowd. The arousal component may therefore be highly
relevant for further investigations, and not only in stroke
populations.

Nadarajah and Goh showed in a recent review that
PSF’s negative effect on patients’ social participation can
be explained by problems with balance self-efficacy. The
VHSQ dizziness component may very well be related
to confidence in balance (self-efficacy), like VHSQ-
dizziness is related to arousal (involving the social par-
ticipation domain of the MFIS), however, this remains to
be tested in future studies.

The association between Cognitive fatigue and gait
speed, may reflect the importance of attention and mental
capacity in gait and posture, as found in other studies.
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Schow et al. suggested that women's reporting of higher levels of fatigue could be explained by endocrine and stress-related factors, however, this will need confirmation in future studies. Like gender, there is no clear evidence of the relation between lesion site and PSF in the literature. Our finding of the association between right hemisphere injury and cognitive fatigue, may be related to the focus of reading and balance problems in this intervention group. However, this has to be tested in larger studies.

Interestingly, we found that treatment time is associated with lower levels of fatigue. This means that the treatment program which the patients received for balance and BVD, seems to have had a positive effect on the level of PSF. Radman et al. found that PSF remains unchanged up to 12 months after stroke supporting our hypothesis that our treatment had a positive effect on levels of fatigue. This may be a result of the association of gender differences in the perception and expression of fatigue as suggested by a study by Falconer M et al. and Nadarajah and Goh. Acciarresi et al. suggested that women's reporting of higher levels of fatigue could be explained by endocrine and stress-related factors, however, this will need confirmation in future studies. Like gender, there is no clear evidence of the relation between lesion site and PSF in the literature. Our finding of the association between right hemisphere injury and cognitive fatigue, may be related to the focus of reading and balance problems in this intervention group. However, this has to be tested in larger studies.

Finally, like other studies we found pain to be associated with fatigue. The type of pain experienced by this patient group were reported in a questionnaire concerning visual problems and are therefore related to their visual problems. Thus, it is most likely that the pain will decrease in line with an improvement of the visual problems and thereby also the PSF. However, this direct association has yet to be tested in further studies.

Ponchel et al. found in a recent review of factors associated with PSF, that 46 studies investigated the association between gender and PSF, and 33 found no association and 12 found a predominance of PSF in females, as supported by our study. This could be related to the experienced feeling of fatigue or it could be a question of gender differences in the perception and expression of fatigue as suggested by a study by Falconer M et al. and Nadarajah and Goh. Acciarresi et al. suggested that women's reporting of higher levels of fatigue could be explained by endocrine and stress-related factors, however, this will need confirmation in future studies. Like gender, there is no clear evidence of the relation between lesion site and PSF in the literature. Our finding of the association between right hemisphere injury and cognitive fatigue, may be related to the focus of reading and balance problems in this intervention group. However, this has to be tested in larger studies.

Figure 4 Association plot between factor scores and balance/gait data (Heat map).

However, Hoang et al. like others failed to find an association between gait and fatigue even if, as suggested by Ponchel et al., it seems obvious that physical fatigue may be more related to balance and gait than cognitive fatigue. The disparity in results may be explained by the different instruments of measurement.
between fatigue and vision and balance/gait. If patients’ symptoms in vision and balance/gait are reduced, they may experience lower level fatigue, and therefore they might not need an intervention for PSF as such.

Conclusion
This present study is, to our knowledge, the first to examine a PCA on MFIS in stroke survivors. We found that MFIS extracted three meaningful components: Cognitive fatigue, Physical fatigue, and Arousal. The arousal component seems important when evaluating PSF, given that arousal was associated with balance impairments and dizziness and symptoms burden of BVD measured by VHISQ. These results open up for further research that would be important for clinical practice.

Limitations
This study was planned as an intervention study, which by its nature challenges patient recruiting. Therefore, we had only a relatively small sample of subjects, resulting in low statistical power. Moreover, we did not explicitly evaluate depression. Since depression has been found to be closely related to PSF. It could have been very relevant to focus on how depression is interrelated with PSF. It could have been very relevant to focus on how depression is interrelated with PSF.

Disclosure Statements
Conflict of Interest
The authors have no conflict of interest in connection with this study.

Funding
This study was carried out with financial support from the Fund for Better Working Environment and the Danish Health Foundation. The authors have no conflict of interest in connection with this study. The ethical declaration of Helsinki has been followed. The project has been approved by the Danish Data Protection Agency j.nr. 2014-41-3324. The authors have no conflict of interest in connection with this study.

ORCID
Trine Schow http://orcid.org/0000-0002-5787-4265

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