

Supplemental Digital Content – Appendices

Løke, Andelic, Helseth, Vassend, Andersson, Ponsford, Tverdal, Brunborg & Løvstad (2022). Stability and change in biopsychosocial factors associated with fatigue 6 and 12 months after traumatic brain injury – an exploratory multilevel study

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S1. Overview of Included Measures

Table S1.1 provides a more detailed overview of all included variables in the study, with level indicators describing at which level the variable is situated. (II) indicates a level 2-variable, meaning that both time points within the individual share the same value on the variable. (I) indicates a level 1-variable, meaning that the variable was measured at both time points, and varies within individuals.

Table S1.1. An overview of all preimary and secondary outcome measures used in our study.	
Constructs	Measure
Fatigue (Primary Outcome)	<p>Fatigue Severity Scale (FSS) (Krupp et al., 1989) (I)</p> <p>Rivermead Post-Concussion Symptoms Questionnaire (RPQ) Fatigue Item (King et al., 1995) (I)</p> <p>Giessen Subjective Complaints List – Fatigue Subscale(Brähler & Scheer, 1995) (I)</p> <p>Chalder Fatigue Questionnaire (CFQ) (Chalder et al., 1993) with subscales for</p> <p>1) Physical Fatigue (I)</p> <p>2) Mental Fatigue (I)</p> <p>3) Total Fatigue (I)</p> <p>Fatigue Factor – estimated with Principal Axis Factoring from items from all fatigue measures (I)</p>
Demographic Variables	<p>Age – centered around the sample mean (II)</p> <p>Sex (Female / Male) (II)</p> <p>Years of Education – centered around the sample mean (II)</p>
Injury Severity Indices	<p>Lowest Glasgow Coma Scale score (G. Teasdale et al., 2014) at injury site or upon admission to the hospital pre-intubation (II)</p> <p>Rotterdam CT Score (Maas et al., 2005) (II)</p> <p>Abbreviated Injury Scale – Head (AIS_head) (Association for the Advancement of Automotive Medicine, 1998) (II)</p> <p>Head Injury Severity Scale (HISS) (Stein & Spettell, 1995) (II)</p> <p>Direct Pathway to Rehabilitation (0/1) (II)</p> <p>Glasgow Outcome Scale (5-level version)(G. M. Teasdale et al., 1998) Upon Discharge from the Acute Hospital (II)</p>

Cognitive Function (Scaled Scores)	WAIS-IV (Wechsler, 2008) Digit Span, with subscale scores for 1) Digit Span Forward Recall (I) 2) Digit Span Backward Recall (I) 3) Digit Span Sequencing Recall (I)
	Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) – Trail Making Test (TMT) with subscales 1) Visual Scanning (I) 2) Number Sequencing (I) 3) Letter Sequencing (I) 4) Number-Letter Sequencing (I) 5) Motor Speed (I) & Color-Word Interference Test (CWIT) with subscales 1) Color Naming (I) 2) Color Reading (I) 3) Color-Word Interference (+ Error Measure) (I) 4) Color-Word Interference – Switching (+ Error Measure) (I)
	WASI (Wechsler, 1999) subscales 1) Similarities (I) 2) Matrix Reasoning (I)
	Conners' Continuous Performance Task (CPT-III) (Conners, 2014) with scaled scores for 1) Hit Reaction Time (HRT) (I) 2) Hit Reaction Time Standard Deviation (HRT SD) (I) 3) Variability (I) 4) Commissions (I) 5) Omissions (I) 6) HRT Block Change (I)

	<p>7) HRT Inter-Stimulus-Interval Change (I)</p> <p>8) Coefficient of Variation (CoV) (calculated independently, raw score) (I)</p> <p>9) 8) Coefficient of Variation (CoV) Block Change (calculated independently, raw score) (I)</p>
Pain Severity	<p>Numerical Rating Scales (0-10) concerning (within the last two weeks) the</p> <p>1) Strongest (I)</p> <p>2) Weakest (I)</p> <p>3) Average (I)</p> <p>4) Current Pain Severity (I)</p>
Pain Dispersion	Pain Drawing (# of Body Regions) (Kuorinka et al., 1987)(I)
Somatic Symptom Burden	<p>Giessen Subjective Complaints List (Brähler & Scheer, 1995)with symptom subscales for</p> <p>1) Musculoskeletal Symptoms (I)</p> <p>2) Gastrointestinal Symptoms (I)</p> <p>3) Cardiovascular Symptoms (I)</p>
Behavioral Inhibition (BIS) & Activation (BAS) Systems	<p>The BIS/BAS Scales (Carver & White, 1994) with subscales scores for</p> <p>1) BAS – Drive (I)</p> <p>2) BAS – Reward Responsiveness (I)</p> <p>3) BAS – Fun Seeking (I)</p> <p>4) Behavioral Inhibition (BIS) (I)</p>
Daytime Sleepiness	Epworth Sleepiness Scale (ESS) (Johns, 1991) (I)
Insomnia Severity	Insomnia Severity Index (ISI) (Bastien et al., 2001) (I)
Psychological Distress	<p>Hopkins Symptoms Checklist (SCL-10) (Derogatis et al., 1974; Strand et al., 2003), with subscales for</p> <p>1) Anxiety (I)</p> <p>2) Depression (I)</p>
Resilience	<p>Resilience Scale for Adults (RSA) (Hjemdal et al., 2011), with subscale scores for</p> <p>1) Planned Future (I)</p> <p>2) Social Competence (I)</p> <p>3) Social Resources (I)</p>

	4) Perception of Self (I)
	5) Structured Style (I)
Five-Factor Personality Traits	<p>NEO Five Factor Inventory 3 (NEO-FFI-3) (McCrae & Costa, 2010) with scaled scores for</p> <p>1) Neuroticism (I)</p> <p>2) Extraversion (I)</p> <p>3) Conscientiousness (I)</p> <p>4) Agreeableness (I)</p> <p>5) Openness (I)</p>
Trait Optimism	Life Orientation Test – Revised, Optimism Subscale (LOT-R) (Scheier et al., 1994) (I)
Loneliness	Three items from UCLA Loneliness Scale 3 (UCLA-LA) (Russell, 1996) (I)

S2. Distributions of Measurement Occasions

As remarked in the main manuscript, restrictions posed by the Covid-19 pandemic meant that some measurements had to be postponed, which led to a higher degree of variability in time between measurements for some patients. For the sake of transparency, histograms are presented here that show the distributions of measurements by months since injury ($\frac{\text{Days Since Injury}}{30}$). In figure S2.1, the time points for all measurements in the first (T1) and second (T2) wave is presented, and finally the time between measurements within subjects is presented in figure S2.2.

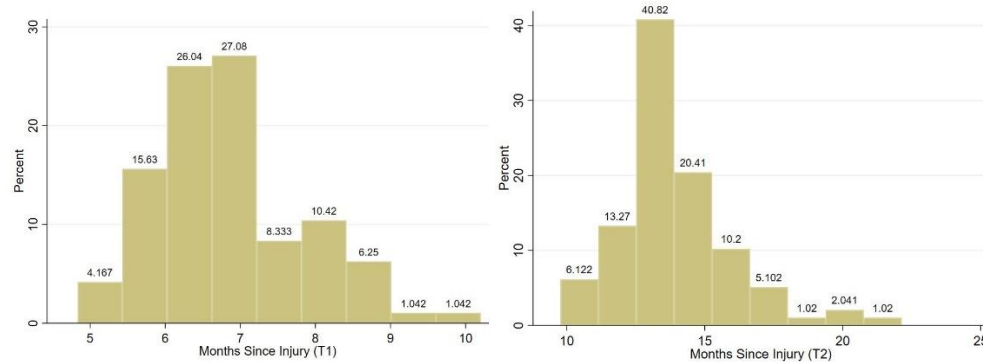


Figure S2.1. The distribution of time since injury (in months) for the first (T1) and second (T2) measurement occasions for all participants. As shown in the latter figure, approximately 20 patients were examined 15 months or more following injury.

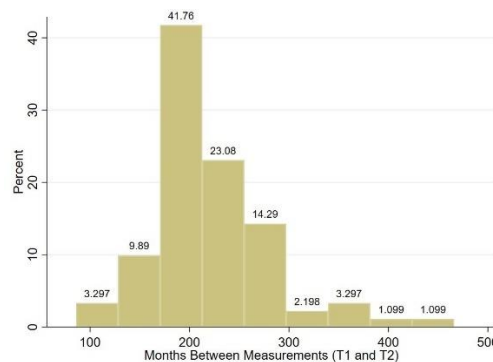


Figure S2.2. Histogram of intervals between measurement occasions for all participants who completed both measurements (in months). Seven patients were examined for their second measurement more than 300 days following their first measurement.

S3. Analyses – Stata Script (with explanatory remarks)

The specific steps of the analyses used in this study is presented in Table S3.1, with additional explanatory comments for the ease of comprehension. Prior to analyses, the data file was transformed from wide format (one row per subject) to long format (two rows per subject). The fatigue factor (primary outcome) was estimated prior to these analyses.

Table S3.1. Overview of specific commands performed both during preliminary exploratory analyses, multilevel factor analyses, and final multilevel regression modelling.

Command	Comment
bysort ID: egen Variable_im = mean(Variable_)	Generate individual aggregate scores within subjects (ID) across both time points for primary outcome and all time-varying associated factors (_im = Individual Mean).
gen Variable_imc = Variable_ - Variable_im	Generate new level 1 scores centered around the individual's mean (_imc = Individual Mean Centered)
pwcorr Fatigue_factor_im Variable_im ..., sig star(.025)	Bivariate correlations between the individual mean scores (Level 2 aggregate) of fatigue and all included variables, with $p < 0.025$ due to the long format of the data.
pwcorr Fatigue_factor_imc Variable_imc ..., sig star(.025)	Bivariate correlations between the scores centered around the individual's mean of fatigue and all included variables, with $p < 0.025$ due to the long format of the data.
factor Variable_im, mineigen(1) blanks(.40) factor Variable_im, factors(3) blanks(.40) rotate, oblimin blanks(.40) factor Variable_im ... (factor 1-3), mineigen(1) blanks(.40) predict (factor 1-3) alpha Variable_im ... (factor 1-3), std	Factor analyses of all significant level 2-variables from prior correlation analyses (individual mean scores). Three factors supported by parallel analyses. Oblimin oblique rotation applied which allows for correlated factors. Three separate factor analyses are conducted for each factor. Reliability (Cronbach's alpha) checked for each factor.
factor Variable_imc, mineigen(1) blanks(.40) factor Variable_imc, factors(1) blanks(.40) predict Change_factor_imc alpha Variable_imc ... , std	Factor analyses of all significant centered level 1-variables from prior correlation analyses (deviation from individual's mean score). One factor supported by parallel analyses.
Mixed Fatigue_factor ID:	Baseline multilevel regression model (variance components model), with Fatigue_factor scores nested within individual subjects.
Mixed Fatigue_factor Age_centered Education_centered Sex Factor_im1 Factor_im2 Factor_im3 Change_factor_imc time_months ID:	Full multilevel regression model with factor scores, demographic variables and time as predictors.

S4. Between- and Within-Subject Factor Loadings

In this section, factor loadings from multilevel factor analyses are presented. Table S4.1 presents the results from the final one-factor between-subject factors (level 2). Note that an initial factor analysis was conducted to evaluate dimensionality and salient loadings, and that the presented loadings are from the resulting one-factor solutions incorporating only variables with salient loadings. Loadings from the level 1 factor is presented in Table S4.2.

Table S4.1. Factor loadings for the final unidimensional factor analyses of between-subject variables associated with fatigue, with reliability estimated with Cronbach's alpha. Factor correlations are presented in the bottom rows. Note that the Injury Severity factor was generated using polychoric factor analysis to allow for adequate calculation of a factor from the ordinal and binary variables. For factor correlations, ^{n.s.} = not significant, *** = $p < 0.001$.

	Factors		
	Psychosocial Robustness	Somatic Vulnerability	Injury Severity
Behavioral Inhibition	-0.52		
Trait Neuroticism	-0.86		
Trait Extraversion	0.76		
Trait Conscientiousness	0.68		
Trait Optimism	0.76		
Loneliness	-0.74		
Anxiety Symptoms	-0.59		
Depressive Symptoms	-0.72		
Resilience – Perception of Self	0.88		
Resilience – Planned Future	0.73		
Resilience – Social Competence	0.70		
Resilience – Structured Style	0.62		
Daytime Sleepiness		0.43	
Insomnia Severity Index		0.59	
Pain – Affected Regions		0.77	
Strongest Pain		0.80	
Weakest Pain		0.74	
Average Pain		0.92	
Current Pain		0.84	
Gastrointestinal Symptoms		0.57	
Musculoskeletal Symptoms		0.90	
Cardiovascular Symptoms		0.61	
AIS_head			0.74
Direct Pathway to Rehabilitation			0.74
Cronbach's alpha	0.92	0.91	0.69
Factor Correlations	1	2	3
1. Psychosocial Robustness	-		
2. Somatic Vulnerability	-0.35***	-	
3. Injury Severity	0.05 ^{n.s.}	0.05 ^{n.s.}	-

Table S4.2. Factor loadings for the final unidimensional factor analyses of within-subject variables associated with within-subject variance in fatigue. Factor reliability was calculated with Cronbach's alpha.

	Correlated Change Factor
Behavioral Inhibition	0.51
Anxiety Symptoms	0.60
Depressive Symptoms	0.68
Strongest Pain	0.49
Average Pain	0.56
Gastrointestinal Symptoms	0.45
Musculoskeletal Symptoms	0.53
Cardiovascular Symptoms	0.54
Cronbach's alpha	0.80

S5. Unique Contributions to Final Regression Model

In order to evaluate the unique contributions to the final regression model with fatigue as primary outcome, post-hoc analyses were conducted. Separate regression models were ran without each significant fixed effect, and estimates were calculated as the difference in explained variance from the final model, as a proportion of baseline variance. Table S5.1 shows the proportion of explained variance by each variable to the final regression model, separated by levels.

Table S5.1. Estimated proportions of variance explained (Quasi- R^2) in fatigue by each variable, separated by levels.

Variable (Level)	Variance Explained (Quasi- R^2)		
	Level 2	Level 1	Total (%)
	Between Subjects (%)	Within Subjects (%)	
Sex (2)	2.6	0.1	2.0
Education (2)	1.9	0.4	1.5
Psychosocial Robustness (2)	4.5	0.6	3.6
Somatic Vulnerability (2)	35.9	-0.7	27.8
Injury Severity (2)	3.9	0.0	3.0
Change Factor (1)	-2.9	17.7	1.7
Months Since Injury (1)	-1.5	6.4	0.2

S6. Post-Hoc Analyses

No common factor could be found to underlie neuropsychological change scores, which may be due to the relatively modest sample size. Post-hoc analyses were conducted to evaluate additional contributions to the final model by changes in performance on single neuropsychological measures. While improvement in several individual measures of neuropsychological functions were univariately associated with decreases in fatigue, models incorporating these variables did not demonstrate significant improvements in model fit, likely due to significant positive correlations between neuropsychological change and time, suppressing the effects of both in the regression model.

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