



Heightened trait and state-level Fatigue and Fatigability in patients with post COVID across cognitive, motor, and emotional domains

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ABSTRACT

Fatigue (self-reported exhaustion) and Fatigability (performance decline) are core symptoms of post COVID but remain poorly understood due to their multidimensional nature. It is unclear how the symptoms manifest at state and trait levels across cognitive, motor, and emotional domains. Our test paradigm included questionnaires addressing cognitively, emotionally and physically perceived Fatigue, and we assessed alertness (cognitive Fatigability), and hand grip strength (motor Fatigability). These were administered before and after experiencing either cognitive (attention tasks) or emotional (short films) load, or relaxation (breathing, virtual reality nature). Compared to healthy controls, patients exhibited significantly elevated trait Fatigue and Fatigability levels, with substantial intra-individual variability in the extent of symptoms. While healthy controls ($n = 58$) responded to acute load with domain-congruent Fatigue, patients with post COVID ($n = 73$) showed amplified state Fatigue and Fatigability interacting across domains, and after either type of loads and relaxation. Our multidimensional paradigm demonstrated that post COVID involves a generalized vulnerability to diverse tasks, even when exposed to relaxing stimuli. To better address symptom heterogeneity, current frameworks of clinical assessments and treatment should differentiate between state and trait Fatigue and Fatigability across cognitive, motor, and emotional domains, while accounting for intra-individual variability through multiple assessments.

1. Introduction

Post COVID-19 condition presents a spectrum of chronic symptoms, with fatigue standing out as one of the most disabling and heterogeneous. Despite its clinical relevance, its complexity leaves substantial gaps in diagnostic and treatment strategies for chronic fatigue symptomatology in post COVID. Against this background, the present study examines Fatigue and Fatigability as multidimensional phenomena that may differ across symptom domains and dynamically change in response to different types of acute load. The World Health Organization

defines post COVID-19 condition (short: post COVID; ICD-10 U09.9) as symptoms that persist or emerge within three months of infection, lasting at least two months, and cannot be explained by alternative diagnoses (World Health Organization, 2019). Globally, over 400 million people are estimated to be affected, with an annual economic burden of \$1 trillion (Al-Aly et al., 2024). Symptoms are heterogeneous, affecting multiple body systems including psychosocial, cardiopulmonary, neuropsychiatric, neuromuscular, and other systemic domains (van den Hout et al., 2024). Among the most frequently reported neuropsychiatric symptoms is “brain fog,” an umbrella term commonly used to

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describe cognitive symptoms such as difficulties with attention, concentration, memory, and executive functioning, represents a key neuropsychiatric symptom and often overlaps with chronic fatigue symptomatology (Davis et al., 2023; van den Houdt et al., 2024). We here focus on chronic fatigue symptomatology, being among the most debilitating symptoms of post COVID, severely reducing patients' health-related quality of life (Walker et al., 2023). Highly heterogeneous and individually fluctuating, chronic fatigue symptoms stand out as complex and insufficiently understood (Davis et al., 2023; Wurz et al., 2022). Current international medical guidelines acknowledge substantial gaps in robust frameworks to guide diagnosis and treatment (Koczulla et al., 2024; World Health Organization, 2023). Addressing symptom heterogeneity is a necessary first step toward developing more precise diagnostics, mechanistic models, and effective treatments for chronic fatigue symptomatology in post COVID.

1.1. Multidimensional Conceptual framework

Recognized as a heterogeneous, non-unitary construct, chronic fatigue has been studied extensively in clinical populations beyond post COVID, such as Multiple Sclerosis (MS) and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Across the literature, established conceptual and assessment approaches make three key distinctions: (a) trait (stable level) versus state (acute response to exertion or load) (Genova et al., 2013) (b) experienced *Fatigue* versus measurable performance declines (i.e., *Fatigability*; Kluger et al., 2013; Stoll et al., 2021), and (c) cognitive and motor domains (Penner et al., 2009). Importantly, we extend this framework by including emotional *Fatigue*, given its prominence in patients' experiences (Wurz et al., 2022), and its recognition in recent guidelines (Koczulla et al., 2024). For an overview of the concept and definitions, see Fig. 1.

Within the concept adopted in our study, we draw a clear conceptual distinction between perceived *Fatigue* and measurable *Fatigability*, in line with established conceptualizations in Multiple Sclerosis (Kluger et al., 2013). Several studies suggest that perceived *Fatigue* and measurable performance decline (*Fatigability*) represent partly overlapping, but distinct constructs, therefore, both levels are important for understanding the full clinical picture of fatigue-related symptomatology (Dettmers et al., 2021; Stoll et al., 2021). In line with studies of Multiple Sclerosis, Fietsam et al. (2023) found evidence for a dissociation between perceived symptoms and measurable performance in a post COVID sample. Specifically, individuals with post COVID reported higher symptom burden on self-report questionnaires, whereas their measured performance in an isokinetic task consisting of 40 consecutive maximal-effort contractions of the knee extensors and flexors did not differ statistically from that of healthy controls. Similar discrepancies between subjective *Fatigue*-related symptoms and objective performance-based measures have also been reported for cognitive performance *Fatigability* and reaction-time based outcomes in

post-COVID samples (Andersson et al., 2025; Zhao et al., 2024).

Further, the distinction between state- and trait-level symptoms is well established (Genova et al., 2013). In the present study, we apply the taxonomy of chronic fatigue proposed for Multiple Sclerosis by Stoll et al. (2021), according to which both perceived *Fatigue* and measurable *Fatigability* may occur at relatively stable trait levels as well as dynamically varying state levels. This distinction is important because current post COVID research, especially large-scale epidemiological studies predominantly employ questionnaires assessing experienced *Fatigue* as a stable trait over extended periods (e.g., van den Houdt et al., 2024). While feasible and informative for capturing symptom burden, trait questionnaires, however, lack accounting for phasic fluctuations. Symptoms vary over time and with context (Bierbauer et al., 2022; Wurz et al., 2022); thus, incorporating situation-specific state measurements is essential to disentangle symptoms and underlying mechanisms. Dynamic changes in perceived *Fatigue* have been documented in post COVID (Tempfli and Randerath, 2025; Wensink et al., 2023), but to our knowledge, no study has yet examined short-term fluctuations in measurable *Fatigability* outcomes, such as alertness reaction times or hand grip strength, across different days in post COVID. Existing longitudinal studies may include repeated assessments over several months (Martin et al., 2024), but they do not capture such day-to-day variability. Addressing this gap, the framework we adapt in the present study distinguishes not only between perceived *Fatigue* and measurable *Fatigability*, but also between trait and state levels within both categories. This is particularly relevant for objective *Fatigability* measures, as performance decline may reflect relatively stable vulnerability to load-related impairment, for example due to persistent structural or functional brain alterations, chronic immune-inflammatory activity, or peripheral muscular changes (Appelman et al., 2024; Douaud et al., 2022; Rudroff et al., 2020). At the same time, measurable *Fatigability* is unlikely to reflect a purely trait-like vulnerability. Consistent with the task-dependency proposed in the model by Rudroff et al. (2020), performance decline may also be shaped by temporally varying contextual and psychophysiological factors, including the specific domain, duration, and intensity of load, sleep quality and circadian rhythm, perceived effort, acute psychosocial stress, and altered interoceptive attention or bodily symptom monitoring (Carnes-Vendrell et al., 2024; Delgado-Sanchez et al., 2023). Accordingly, measurable *Fatigability* outcomes may be best understood as arising from an interaction between relatively stable vulnerability to load-related impairment (trait-level) and state-dependent factors that fluctuate across situations and days. To allow for these dynamics conceptually, our framework therefore distinguishes not only between perceived *Fatigue* and measurable *Fatigability*, but also between trait and state levels within both. It should be noted that, although the distinction between perceived and measurable symptoms at trait and state levels is well established in the chronic fatigue literature, taxonomies differ across models. For example, Enoka et al. (2021) proposed a Multiple Sclerosis

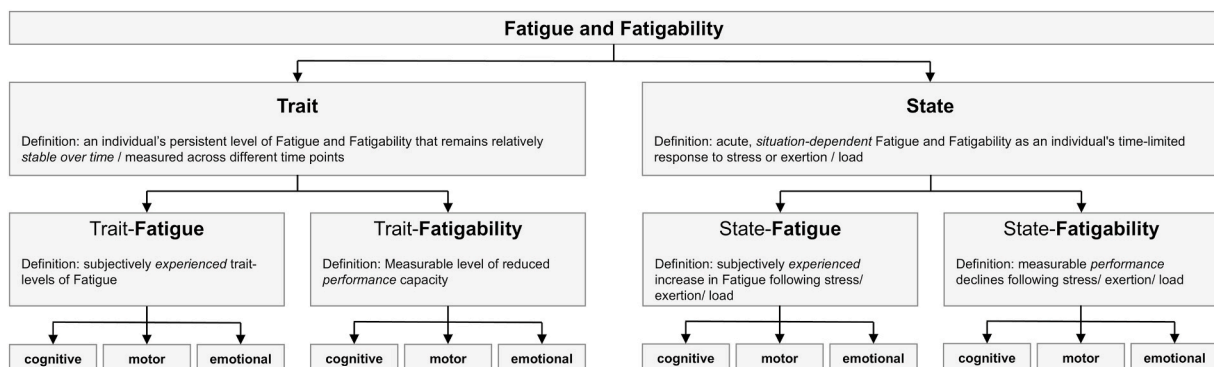


Fig. 1. Multidimensional concept of Fatigue and Fatigability.

framework that integrates pathophysiological mechanisms but uses a different terminology.

State Fatigue and Fatigability are commonly assessed comparing symptoms pre and post experimental load. Hand grip strength is used as a marker of motor Fatigability: in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), hand grip strength after rest was significantly lower than in healthy controls (Jakel et al., 2021), and in post COVID, reduced grip strength correlated with biomarkers of muscular exhaustion (Kedor et al., 2022). Alertness, typically measured via reaction-time tasks, is an established measure for cognitive Fatigability (Charles James et al., 2025). There is a lack of studies investigating reaction-time changes as an acute response to load in post COVID. In MS, load paradigms showed that cognitive load reduced alertness relative to controls (Neumann et al., 2014) and increased cognitive Fatigability and Fatigue after cognitive, but not relaxation tasks (Stoll et al., 2021). Moreover, increases followed both cognitive and motor loads, with stronger effects after cognitive load (Claros-Salinas et al., 2013). These findings are particularly interesting as they suggest that acute Fatigue and Fatigability responses are task-dependent and may involve cross-domain interactions. These findings are consistent with the post-COVID fatigue model proposed by Rudroff et al. (2020), which emphasizes task dependency as an important factor. In line with this perspective, our comprehensive test concept was designed to systematically examine Fatigue and Fatigability responses across tasks with different demands (cognitive load, emotional load, and relaxation) in order to better understand the influence of load type of the performed task and domain-specific effects.

1.2. Current study

Taken together, literature shows that chronic fatigue symptoms are observed at trait and state levels, across cognitive, emotional, and motor domains, both measurable and subjectively reported - depicting a multidimensional rather than unitary construct. Yet studies have largely examined the dimensions selectively. We translate the multidimensional framework (Fig. 1) into a single experimental paradigm to differentiate facets of Fatigue and Fatigability in post COVID and compare them to a healthy control group. To account for the state-level, we systematically compare Fatigue and Fatigability responses before and after cognitive load and emotional activation, allowing us to examine potential cross-domain interactions. In addition, we included a relaxation control condition, consisting of paced breathing and a 360° virtual-reality nature scene, to contextualize the effects of cognitive and emotional load. This protocol has previously shown subjective and physiological relaxation effects in healthy students and in individuals with borderline personality disorder (Gaertner et al., 2024, 2025). Trait-levels are assessed via questionnaires and multiple baseline measurements. To our knowledge, no post COVID study has simultaneously examined state-level Fatigue with cognitive and motor Fatigability in one framework, nor incorporated emotional content as experimental load.

The present study aims to investigate how Fatigue and Fatigability in patients with post COVID respond to different types of acute load (cognitive, emotional, and a control condition involving relaxation), in comparison to healthy controls. We expect both baseline levels and pre-to-post changes to be affected across multiple dimensions. For the trait level, we hypothesize that patients with post COVID will have higher cognitive, emotional, and motor Fatigue, as well as lower alertness and hand grip strength when compared to healthy controls at baseline. Our second hypothesis addresses the state level: Pre-to-post-changes in cognitive, emotional, and motor Fatigue, as well as alertness and hand grip strength will differ between groups (patients with post COVID and healthy controls) and conditions (cognitive load, emotional activation, relaxation). Compared to controls, we expect patients with post COVID to show more pronounced changes towards lower performance and higher experienced Fatigue.

Integrating the key dimensions within a comprehensive framework,

the present study offers an opportunity to capture the multifaceted nature of Fatigue and Fatigability in patients with post COVID, reveal potential interactions between symptom domains, and inform the development of targeted diagnostic and therapeutic strategies.

2. Methods

2.1. Sample

All participants gave written consent prior to participating in this study. All procedures were approved by the Ethics Committee of the University of Konstanz (approval no 40/2021) and conducted in accordance with the Declaration of Helsinki.

2.1.1. Power analysis

An ad-hoc power analysis using G*Power 3.1 (Faul et al., 2009) was conducted to estimate required sample sizes for pre-post comparisons. For changes in alertness reaction times, assuming a medium effect (Cohen's $d = 0.51$; Stoll et al., 2021), a one-tailed Wilcoxon signed-rank test with $\alpha = .05$ and power = 0.95 required at least 45 participants in the clinical group. For hand grip strength, using effect sizes ($d = 0.55$) derived from Jakel et al. (2021), the required sample size was 39 participants.

2.1.2. Sample characteristics

Between October 2022 and May 2024, all patients admitted to the neurological rehabilitation clinic (Kliniken Schmieder, Konstanz, Germany) with a diagnosis of post COVID-19 condition (ICD-10 U09.9) were invited to participate voluntarily and without monetary compensation. Of 132 in-patients meeting inclusion criteria (signed consent, native-level German, normal or corrected vision and hearing, no documented cerebral lesion), 32 (24%) dropped out due to reduced exertion tolerance, 27 (20%) for predominantly organizational reasons (e.g., early discharge). The final post COVID sample comprised 73 patients completing all three experimental sessions. Comorbidities are detailed in Supplementary Table S1. Healthy control participants were recruited between May 2023 and November 2024 via public advertisements and participant databases maintained by associated research groups at the University of Konstanz (Germany) and the University of Vienna (Austria). Additional exclusion criteria were: neurological or psychiatric history, diabetes, acute illness or injury, and SARS-CoV-2 infection or vaccination within the last three months. Of the 67 healthy controls, nine (13%) dropped out for non-exertion-related reasons (no-shows to subsequent appointments), resulting in 58 complete datasets. The healthy control group was pre-screened to match the post-COVID group by age (± 10 years) and sex and received €10/hour compensation. No group differences were observed in age, sex, or education (see Table 1).

2.2. Multidimensional framework of fatigue and fatigability

The underlying framework distinguishes Fatigue from Fatigability and trait from state levels (Fig. 1), across cognitive, motor, and emotional domains (see Supplementary Table 2). To explore its multidimensional nature, we conducted Spearman rank correlations separately for the post COVID and healthy control groups. Overall, the results are consistent with the proposed multidimensional framework, while further validation with larger sample sizes is needed (for details see Supplemental File S6).

2.3. Procedure

The procedure was delivered by trained personnel with a psychological background. Eleven psychologists or advanced psychology students conducted sessions after structured training, with initial ongoing supervision by a psychological psychotherapist and licensed neuropsychologist.

Table 1
Sample characteristics.

Characteristic	Post COVID N = 73	Healthy controls N = 58	Test	Statistic	p
Age			Mann-Whitney-U	$U = 1771$	0.109
Mean (SD)	49.1 (14.5)	44.9 (14.5)			
Range	27.0–70.0	20.0–72.0			
Biological sex			Chi-squared	$\chi^2 = 1.05$	0.306
Male	18 (24.7%)	19 (32.8%)			
Female	55 (75.3%)	39 (67.2%)			
Education			Chi-squared	$\chi^2 = 0.18$	0.669
≤12 years	13 (17.8%)	12 (20.7%)			
>12 years	50 (68.5%)	38 (65.5%)			
Missing	10 (13.7%)	8 (13.8%)			
Virus variant^a			Chi-squared	$\chi^2 = 10.89$	0.028*
Alpha	22 (30.1%)	9 (15.5%)			
Delta	10 (13.7%)	3 (5.2%)			
Omicron BA.2	27 (37.0%)	19 (32.8%)			
Omicron BA.5	7 (9.6%)	6 (10.3%)			
Omicron XBB.1.5	0 (0.0%)	5 (8.6%)			
Missing	7 (9.6%)	16 (27.6%)			
Infection count			Chi-squared	$\chi^2 = 17.40$	0.001***
0	0 (0.0%)	9 (15.5%)			
1	41 (56.2%)	33 (56.9%)			
2	21 (28.8%)	11 (19.0%)			
3	6 (8.2%)	0 (0.0%)			
Missing	5 (6.8%)	5 (8.6%)			
Hospitalized			Fisher-Exact-Test		0.247
Not hospitalized	63 (86.3%)	58 (100.0%)			
Hospitalized	3 (4.1%)	0 (0.0%)			
Missing	7 (9.6%)	0 (0.0%)			
Vaccination Count			Chi-squared	$\chi^2 = 7.76$	0.101
1	1 (1.4%)	3 (5.2%)			
2	10 (13.7%)	6 (10.3%)			
3	23 (31.5%)	24 (41.4%)			
4	3 (4.1%)	13 (22.4%)			
Not vaccinated	4 (5.5%)	3 (5.2%)			
Missing	32 (43.8%)	9 (15.5%)			
PEM screening^b			Chi-squared	$\chi^2 = 104.42$	< 0.001***
Negative (no PEM)	5 (6.8%)	54 (93.1%)			
Positive (PEM)	64 (87.7%)	0 (0.0%)			
Missing	4 (5.5%)	4 (6.9%)			

Note. Self-reported data.

^a Virus variants based on self-reported date of first infection, and predominant variant distributions in Germany, as published by the [Robert Koch Institute, 2025](#).

^b Post-exertional malaise (PEM), DePaul Symptom Questionnaire (DSQ; [Cotler et al., 2018](#)).

2.3.1. Assessment of State Fatigue and Fatigability

Measurements were obtained before (baseline) and after three controlled experimental conditions: cognitive load, emotional activation, relaxation (control). For an overview see [Fig. 2](#).

Fatigue and Fatigability Measures. Pre- and post-load, cognitive, emotional, and motor Fatigue were recorded with the German version of the *Questionnaire on Perceived Load and Fatigue - State* (QLF-S, [Tempfli et al., 2022](#); English version: [Tempfli et al., 2025](#)). The following three items were included: “At the moment I feel cognitively fatigued”; “At the moment I feel physically fatigued”; and “At the moment I feel emotionally fatigued”, rated on visual analogue scales from 0 = “not at all” to 10 = “very intense”. Cognitive Fatigability was measured using the alertness subtest of the Test Battery for Attentional Assessment (TAP; [Zimmermann and Fimm, 2017](#)) with the median reaction time condition (without warning tone) as the metric (in ms). Alertness reaction time without a warning signal, particularly when assessed with the standardized TAP battery, represents an established approach to measuring cognitive Fatigability. It has long been applied in multiple sclerosis research ([Claros-Salinas et al., 2013](#); [Stoll et al., 2021](#)) and has more recently been translated to post-COVID populations ([Hasting et al., 2023](#); [Seibert et al., 2025](#)). Motor Fatigability was assessed through hand grip strength following the Southampton protocol described by [Roberts et al. \(2011\)](#), utilizing the maximum value obtained from three measurements per hand (in kg). Hand grip strength has also been used as an indicator of motor Fatigability or physical functioning in ME/CFS and post-COVID research. In these populations, reduced grip strength has

been associated with greater disability and symptom severity, functional impairment, and biomarkers linked to symptom burden ([Kedor et al., 2022](#); [Paffrath et al., 2024](#)).

Load Conditions. The study used a mixed repeated-measures design, with group (post-COVID patients vs. healthy controls) as a between-subject factor and load condition (cognitive, emotional, relaxation) and time (pre-vs. post-load) as within-subject factors. Each participant in both the analyzed post COVID and healthy control samples completed all three 80-min sessions, each including the specific load induction (35 min), instructions, training trials, questionnaires, and cardiovascular preparations. Sessions were performed on separate days (≥72-h in between) in varying order. Within the post COVID sample, session order was not randomized but adapted to organizational constraints, e.g., therapy schedules. The session order of the healthy control group was then matched to the post COVID group.

Condition A (Cognitive Load). Subtests of a standardized test battery were presented (TAP; [Zimmermann and Fimm, 2017](#)) including working memory, sustained attention, and divided attention.

Condition B (Emotional Activation). Two animated short films with emotive music and no spoken dialogue were used to activate emotions. *Canvas* ([Abney, 2020](#)) shows a grandfather and grandchild coping with grief through painting, while *If Anything Happens I Love You* ([McCormack and Govier, 2020](#)) portrays parents coping with the loss of their child after a school shooting. Participants received a trigger warning before the second film and could opt out; none did.

As a manipulation check for the emotional activation, participants’

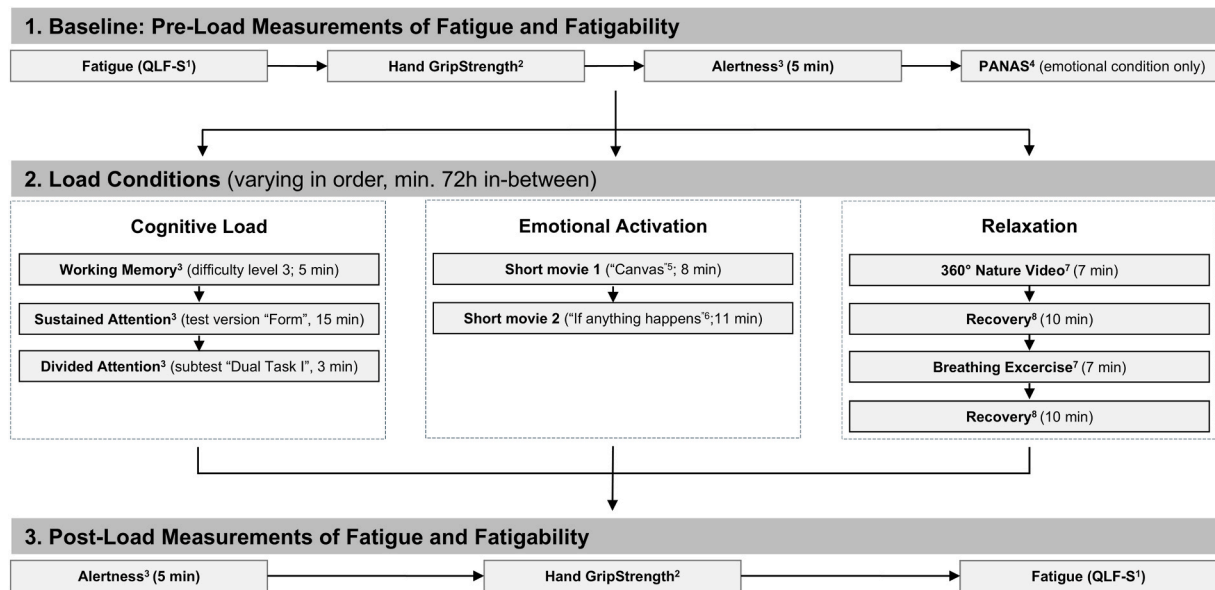


Fig. 2. Study Design

Note. For full study design see Tempfli et al. (2025). The study used a mixed repeated-measures design. All participants in both groups (post-COVID patients: $n = 73$; healthy controls: $n = 58$) completed all three load conditions (cognitive, emotional, relaxation) in separate sessions. Sessions were scheduled on separate days with at least 72 h between sessions. Session order was adapted to organizational constraints in post-COVID patients and matched in healthy controls. ¹Questionnaire on Perceived Load and Fatigue - State (Tempfli et al., 2022); ²Southampton protocol (Roberts et al., 2011); ³Test Battery for Attentional Assessment (Zimmermann and Fimm, 2017); ⁴Positive and Negative Affect Schedule (Breyer and Bluemke, 2016); ⁵Canvas (Abney, 2020); ⁶If anything happens (McCormack and Govier, 2020); ⁷Gaertner et al. (2024); ⁸optional coloring mandalas or reading newspapers.

affect was assessed using the Positive and Negative Affect Schedule (PANAS; Breyer and Bluemke, 2016) before load, after the first, and the second film. Separate 2×3 mixed ANOVAs were conducted for positive and negative affect, with Group (post COVID vs. healthy control) as a between-subjects factor and Time (pre-load, post-film1, post-film2) as a within-subjects factor. For positive affect, main effects of Group ($F(1, 117) = 5.63, p = .019, \eta^2 = 0.038$), and Time ($F(1.62, 189.32) = 34.83, p < .001, \eta^2 = 0.050$) were significant; the interaction was not ($F(1.62, 189.32) = 0.04, p = .936$). For negative affect, both Group ($F(1, 115) = 9.56, p = .003, \eta^2 = 0.063$), and Time ($F(1.41, 161.93) = 53.21, p < .001, \eta^2 = 0.083$) were significant; the interaction was non-significant ($F(1.41, 161.93) = 1.95, p = .158$). In conclusion, although patients and controls differed in overall affect levels, both groups showed comparable change patterns (positive affect decreased, negative increased), indicating that, in both groups, the emotional load manipulation altered affect as intended. Equivalent results were obtained using nonparametric tests.

Condition C (Relaxation). As a control condition, the relaxation condition included paced breathing and a 360° virtual reality nature video, following the procedure developed by Gaertner et al. (2024). The order of the two elements was counterbalanced and matched between groups. After each element, participants completed a 10-min recovery phase during which they could color or read.

2.3.2. Assessment of Trait Fatigue and Fatigability

As illustrated in Fig. 2, Fatigue and Fatigability were assessed before (baseline) and after three load conditions (cognitive, emotional, relaxation) conducted on separate days. Trait-level measures are defined in Supplementary Table 2. The mean of the three baseline values of the Fatigue and Fatigability measures (alertness, hand grip strength, cognitive, emotional and motor fatigue) served as an indicator for trait-level symptoms. During rehabilitation, patients completed questionnaires including sociodemographic items, and the Fatigue Scale for Motor and Cognitive Functions (FSMC; Penner et al., 2009), an established questionnaire for the assessment of cognitive and motor Fatigue. Since it assesses Fatigue additionally on an emotional subscale, we

included the Burnout Screening Scales (BOSS II; Geuenich and Hagemann, 2014). The DePaul Symptom Questionnaire (DSQ; Cotler et al., 2018) was used to assess post-exertional malaise. Healthy controls completed the same questionnaires at home. This study forms part of the broader multiFACE Study; full protocol details are reported in Tempfli et al. (2025).

2.4. Statistics and data analysis

Analyses were conducted in R version 4.4.3 (R Core Team, 2025) using RStudio (version 2024.12.1.563). Graphs were created using ggplot2 version 3.5.1 (Wickham, 2016). The significance level was set at $\alpha = .05$, and we performed Bonferroni-Holm correction for multiple testing. Missing data ranged from 0.3% to 3.3% across variables, and no imputation was performed. Cases with missing values were excluded only from the respective sub-analyses. AI-based technology (OpenAI, 2026) was used to assist with copy editing and R code optimization. All decisions, study design, literature research, manuscript drafting, hypotheses, analyses, results, interpretations, conclusions, limitations, and implications of the study were made by the authors. The statistical approach, including analytical procedures, model specifications, and correction methods, was predefined by the authors. AI-assisted code suggestions were not used in an automated manner but were reviewed, adapted, and, where necessary, manually revised by the authors. The optimized code was checked for correct implementation of the intended analyses, including case inclusion, variable recoding, model specification, and correction procedures. Results were verified through targeted manual calculations and plausibility checks based on descriptive graphs and raw-data tables.

2.4.1. Trait-level: group comparisons of baseline scores

Per individual, the mean of the three baseline values of Fatigue (cognitive, emotional, and motor Fatigue) and Fatigability measures (alertness, hand grip strength) served as measures for the trait-level. Complemented by the FSMC (Penner et al., 2009) and BOSS-II (Geuenich and Hagemann, 2014), trait measures were compared

between patients and controls using Mann–Whitney *U* tests.

2.4.2. State-level: Linear mixed models for change scores

In line with our definitions (Supplementary Table 2), state Fatigue and Fatigability were operationalized as pre–post changes. Higher change scores consistently indicate higher Fatigue or Fatigability, calculated as post–pre differences for all variables except hand grip strength, for which subtraction was reversed (pre–post) to maintain interpretive consistency. Following Brown (2021) and Meteyard and Davies (2020), linear mixed-effects models were computed to examine the effects of group (post COVID: PC; healthy control: HC), load condition (cognitive, emotional, relaxation), and their interaction on change scores, including age and sex as covariates and random intercepts by participant ($N = 393$ observations across 131 codes):

$$\text{change scores} \sim 1 + \text{age} + \text{sex} + \text{group} + \text{condition} + \text{group:condition} + (1|\text{code})$$

Random slopes could not be modeled due to the data structure: each participant contributed only one observation per condition, resulting in convergence issues in random slope models. We built our model based on our research question and ad-hoc hypotheses and entered all predictors, interaction, and co-variables (age and sex) at once into the model. Dummy coding was applied with the relaxation condition in the healthy control group as the reference level. One-tailed *p*-values were used for the directed hypotheses on fixed effects; two-tailed *p*-values for covariates and random intercepts. Intraclass correlation coefficients (ICC) were computed as the ratio of intercept variance to total variance, with $\text{ICC} > 0.30$ considered high (Pillinger, 2025).

Because the data exhibited pronounced skewness and outliers, violating assumptions of classical linear mixed models (LMMs), models were first estimated using lme4's lmer-function version 1.1.36 (Bates et al., 2015), and then re-estimated with robust linear mixed effects modeling with robustlmm version 3.3.1 (Koller, 2016). The pattern of significant predictors was consistent across methods, except that age reached significance only in the robust model for alertness change. The robust models, however, estimated zero variance for the random intercepts, a result inconsistent with descriptive statistics and classical LMM estimates. Following Meteyard and Davies (2020), we interpret this as likely reflecting convergence issues or overcorrection by the robust algorithm, possibly due to the limited number of observations per participant ($n = 3$). Given these concerns, classical LMM results are reported in the main text, with robust model results provided in

Supplementary Table S3.

3. Results

3.1. Trait-level differences

In order to assess pathological symptom load at trait levels in patients with post COVID, we compared their symptom levels to healthy controls. Mann–Whitney-*U* tests revealed significant group differences in trait-level and mean baseline values for all Fatigue and Fatigability outcomes. In line with our hypotheses, patients with post COVID showed significantly higher trait Fatigue and Fatigability in all performed measures, yielding medium to large effect sizes. The median FSMC scores of the post COVID group (PC) exceeded the cut-off for severe cognitive and motor Fatigue, whereas the healthy control group (HC) showed no abnormal values. For details, see Table 2.

Within the post COVID group, no significant differences emerged between the three baseline assessments, i.e., before cognitive load, emotional activation, and relaxation; the same pattern was observed for healthy controls (Supplementary Table S4). To assess intraindividual differences in baseline Fatigue and Fatigability (Fig. 3), we performed a post-hoc analysis computing within-person standard deviations across the three pre-load measures (cognitive load, emotional activation, and relaxation). These intraindividual standard deviations were then compared between the post COVID and healthy control group using Mann–Whitney *U* tests (Supplementary Table S5). Across all variables, patients with post COVID showed significantly higher within-person variability at baseline than healthy controls, with effect sizes ranging from 0.22 to 0.58, calculated as $r = Z/\sqrt{n}$ (Fritz et al., 2012). These group comparisons demonstrate that patients with post COVID showed significantly higher trait Fatigue and Fatigability than healthy controls across all measures, accompanied by less stable symptom expression.

3.2. State-level: change scores

In order to examine whether load conditions affect healthy controls and patients differently, we compared the change in Fatigue and Fatigability from pre-to post cognitive, emotional or relaxation conditions, respectively. On state-levels, we expected pre-to-post-changes in Fatigue and Fatigability measures to be more pronounced in patients with post COVID in all conditions (cognitive load, emotional activation, relaxation). Hypothesized fixed effects were tested directionally; covariates

Table 2

Trait Fatigue and Fatigability: Between-group comparisons of trait Fatigue and baseline state measures averaged across the three pre-load assessments.

Outcome	N_{total}	Post COVID (PC)		Healthy control (HC)		U	p	p_{adj}^a	ES^b
		n_{PC}	Mdn_{PC}	n_{HC}	Mdn_{HC}				
Cognitive domain									
Alertness (Fatigability)	131	73	292.3	58	241.8	3256.5	<0.001	<0.001***	0.46
Cognitive Fatigue	131	73	3.8	58	0.3	3765.5	<0.001	<0.001***	0.67
FSMC _{cognitive}	122	69	40	53	13	3503.0	<0.001	<0.001***	0.78
BOSS _{cognitive}	123	70	2.5	53	0.3	3543.0	<0.001	<0.001***	0.78
Motor domain									
Hand grip (Fatigability)	131	73	25.7	58	30.1	1364.0	<0.001	<0.001***	0.30
Motor Fatigue	131	73	3.8	58	0.3	3814.5	<0.001	<0.001***	0.69
FSMC _{motor}	122	69	40	53	13	3514.5	<0.001	<0.001***	0.79
BOSS _{motor}	123	70	2.2	53	0.2	3628.5	<0.001	<0.001***	0.82
Emotional domain									
Emotional Fatigue	131	73	2.3	58	0.2	3494.0	<0.001	<0.001***	0.56
BOSS _{emotional}	123	70	1.7	53	0.2	3226.0	<0.001	<0.001***	0.63

Note. For alertness [ms], hand grip strength [kg], and cognitive, motor, and emotional Fatigue (QLF-S; Tempfli et al., 2022), subject-level means of all three baseline observations were compared between post COVID (PC) and healthy controls (HC) using Mann–Whitney *U* tests. BOSS_{cognitive}, BOSS_{motor}, BOSS_{emotional}: The subscales for cognitive, motor, and emotional Fatigue of the Burnout Screening Scales II (BOSS II, Geuenich and Hagemann, 2014). FSMC_{cognitive}, FSMC_{motor}: the subscales for cognitive and motor Fatigue of the Fatigue Scale for Motor and Cognitive Functions (FSMC, Penner et al., 2009), severe Fatigue cut-offs: FSMC_{cognitive} ≥ 34 ; FSMC_{motor} ≥ 32 .

^a Bonferroni-Holm-adjusted.

^b Effect sizes: $r = Z/\sqrt{n}$ (Fritz et al., 2012).

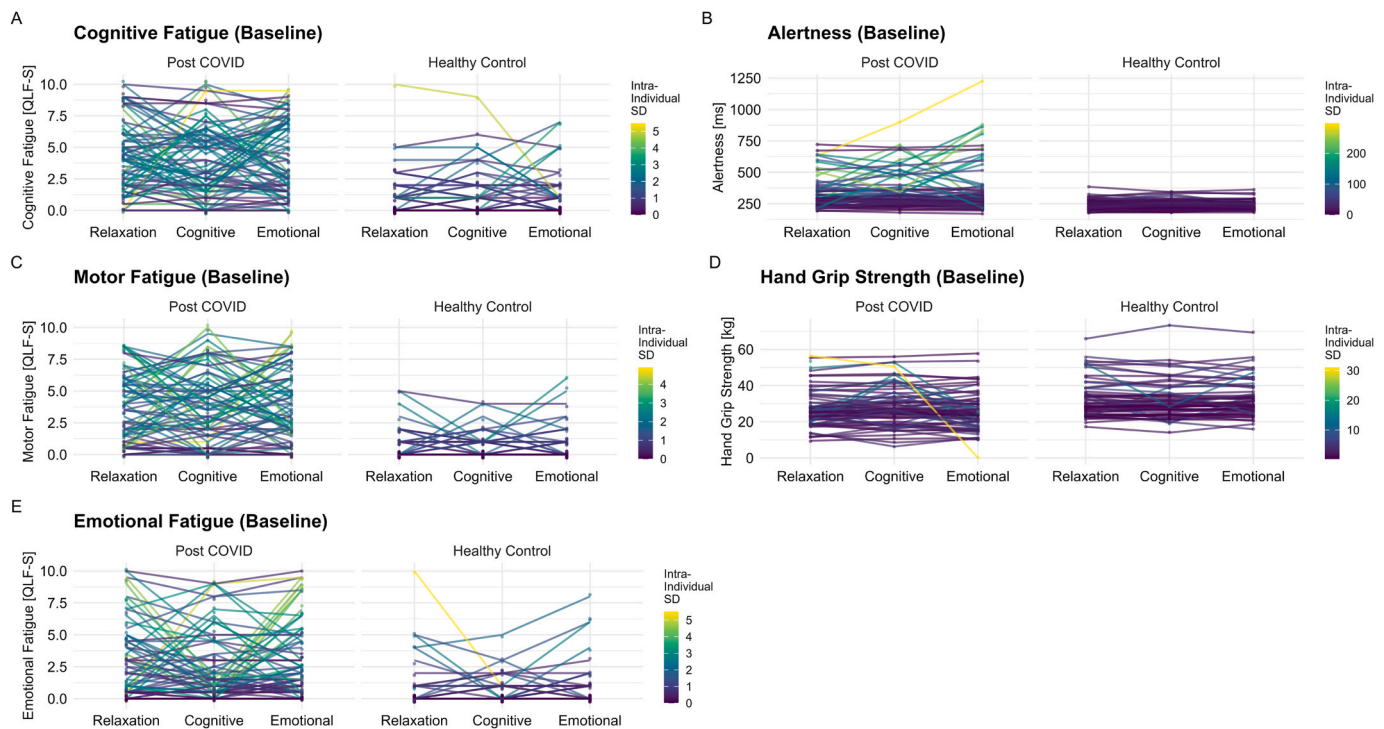


Fig. 3. Trait Fatigue and Fatigability: Baseline Measures and Within-Person Variability (SD) of Fatigue and Fatigability Across Conditions

Note. For each participant, intraindividual standard deviations across the three baseline measurement time points (cognitive load, emotional activation, relaxation) were calculated and are visualized in the line plots. Color gradients represent the magnitude of intraindividual variability, scaled within each variable from the observed minimum to the maximum across all participants. Therefore, color intensity should be interpreted within panels only and not compared directly across different outcome variables. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and random intercepts were evaluated using two-tailed tests. The results of our performed linear mixed models are summarized in Table 3 and visualized in Fig. 4.

3.2.1. Cognitive fatigue

We expected changes in cognitive Fatigue to depend on the load condition (cognitive load, emotional load or relaxation condition) and to be more pronounced in the post COVID group than in the healthy control group. Accordingly, the linear mixed model showed a significant simple effect of cognitive load within the healthy control group: While, indicated by the significant negative intercept, healthy controls showed reduced cognitive Fatigue after relaxation, cognitive load substantially intensified cognitive Fatigue. We did not find a significant simple effect of emotional activation.

According to our hypothesis, we found a significant simple effect of the post COVID group, meaning that after the relaxation condition (reference level), patients experienced a significant increase in cognitive Fatigue compared to healthy controls. The significant interaction between the post COVID group and cognitive load suggests that in the post COVID group, cognitive Fatigue increased more after cognitive load than after relaxation, and that this effect was more pronounced in patients than in healthy controls. There was no significant interaction of the post COVID group and emotional activation, indicating comparable changes after the emotional activation condition and the relaxation condition.

3.2.2. Cognitive Fatigability (alertness)

In line with our hypotheses, patients with post COVID exhibited a markedly greater increase in cognitive Fatigability following cognitive load compared to healthy controls, as indicated by the significant interaction between the post COVID group and cognitive load. The model for change in alertness reaction times showed no other significant effects but revealed a high intraclass correlation for random intercepts

by code ($ICC_{\text{alertness}} = 0.358$), indicating substantial clustering by individuals. This suggests that variance in alertness reaction time changes could be substantially attributed to individual differences.

3.2.3. Motor fatigue

Contrary to our hypotheses, none of the predictors for the change in motor Fatigue reached statistical significance.

3.2.4. Motor Fatigability (hand grip strength)

We hypothesized that changes in motor Fatigability, operationalized by the change in hand grip strength, would differ between groups and conditions. Accordingly, we found a significant simple effect for the post COVID group, indicating that after the relaxation condition, patients demonstrated a greater decrease in hand grip strength compared to healthy controls. However, the model did not reveal any further significant simple effects or interactions, indicating that the pattern of higher decrease in the patient group did not significantly differ after relaxation, cognitive load, and emotional activation.

3.2.5. Emotional fatigue

As hypothesized, the model for changes in emotional Fatigue revealed differences between groups and conditions. We found a significant negative intercept, indicating that healthy controls experienced a decrease in emotional Fatigue after relaxation. The session with emotional activation produced a significant increase in emotional Fatigue in the healthy control group (simple effect of the emotional activation). Interactions between the post COVID group and both cognitive load and emotional activation were significant. These findings suggest that patients show an especially pronounced increase in emotional Fatigue when challenged under both cognitive and emotional conditions. Specifically, the significant interaction between the post COVID group and emotional activation demonstrates an additional heightened emotional Fatigue response in patients with post COVID compared to

Table 3

Linear mixed-effects models predicting pre-to post-change scores in state fatigue and fatigability by group and load condition.

Cognitive Fatigue						
Fixed Effects	Estimate	SE	95% CI		t Value	p Value
			LL	UL		
Intercept	−1.142	0.568	−2.255	−0.029	−2.012	0.044*
Age	0.011	0.010	−0.009	0.031	1.098	0.272
Sex	0.412	0.269	−0.114	0.938	1.535	0.062
PC Group	1.241	0.400	0.458	2.025	3.105	0.001***
Cognitive Condition	1.707	0.404	0.916	2.498	4.231	<0.001***
Emotional Condition	0.576	0.402	−0.211	1.363	1.435	0.076
PC Group x Cognitive Condition	0.952	0.540	−0.107	2.012	1.762	0.039*
PC Group x Emotional Condition	0.032	0.541	−1.028	1.092	0.059	0.476
Random Effects	Variance	SD	ICC			
Code (Intercept)	0.343	0.586	0.07			
Residual Variance	4.542	2.131				
Cognitive Fatigability (Alertness)						
Fixed Effects	Estimate	SE	95% CI		t Value	p Value
			LL	UL		
Intercept	−11.815	29.482	−69.598	45.969	−0.401	0.689
Age	0.157	0.555	−0.931	1.245	0.283	0.777
Sex	15.931	15.094	−13.653	45.515	1.055	0.146
PC Group	27.239	18.144	−8.321	62.800	1.501	0.067
Cognitive Condition	0.534	15.197	−29.251	30.320	0.035	0.486
Emotional Condition	−1.422	15.197	−31.208	28.363	−0.094	0.537
PC Group x Cognitive Condition	73.199	20.397	33.221	113.176	3.589	<0.001***
PC Group x Emotional Condition	11.422	20.358	−28.478	51.322	0.561	0.287
Random Effects	Variance	SD	ICC			
Code (Intercept)	3736.359	61.126	0.358			
Residual Variance	6697.301	81.837				
Motor Fatigue						
Fixed Effects	Estimate	SE	95% CI		t Value	p Value
			LL	UL		
Intercept	−0.455	0.525	−1.483	0.573	−0.867	0.386
Age	−0.001	0.009	−0.019	0.018	−0.059	0.953
Sex	0.268	0.249	−0.221	0.756	1.075	0.141
PC Group	0.443	0.366	−0.275	1.161	1.209	0.113
Cognitive Condition	0.582	0.367	−0.137	1.301	1.588	0.056
Emotional Condition	0.127	0.365	−0.588	0.843	0.349	0.364
PC Group x Cognitive Condition	0.107	0.491	−0.856	1.069	0.217	0.414
PC Group x Emotional Condition	0.024	0.492	−0.939	0.987	0.049	0.480
Random Effects	Variance	SD	ICC			
Code (Intercept)	0.351	0.593	0.086			
Residual Variance	3.749	1.936				
Motor Fatigability (Hand Grip Strength)						
Fixed Effects	Estimate	SE	95% CI		t Value	p Value
			LL	UL		
Intercept	0.945	0.743	−0.512	2.402	1.271	0.204
Age	0.000	0.013	−0.026	0.027	0.026	0.979
Sex	−0.257	0.367	−0.976	0.461	−0.702	0.759
PC Group	1.560	0.518	0.545	2.575	3.013	0.001**
Cognitive Condition	−0.655	0.511	−1.656	0.346	−1.283	0.900
Emotional Condition	−0.338	0.511	−1.339	0.663	−0.662	0.746
PC Group x Cognitive Condition	−0.114	0.685	−1.457	1.229	−0.167	0.566
PC Group x Emotional Condition	−0.284	0.684	−1.625	1.057	−0.415	0.661
Random Effects	Variance	SD	ICC			
Code (Intercept)	0.982	0.991	0.115			
Residual Variance	7.562	2.750				
Emotional Fatigue						
Fixed Effects	Estimate	SE	95% CI		t Value	p Value
			LL	UL		
Intercept	−1.622	0.601	−2.800	−0.444	−2.699	0.007**
Age	0.022	0.011	0.001	0.044	2.071	0.038*
Sex	0.744	0.291	0.174	1.314	2.559	0.005**
PC Group	0.483	0.404	−0.308	1.275	1.197	0.116
Cognitive Condition	0.398	0.389	−0.364	1.160	1.024	0.153
Emotional Condition	1.129	0.387	0.372	1.887	2.921	0.002**
PC Group x Cognitive Condition	1.132	0.521	0.111	2.152	2.174	0.015*
PC Group x Emotional Condition	1.173	0.521	0.152	2.194	2.251	0.012*
Random Effects	Variance	SD	ICC			
Code (Intercept)	0.783	0.885	0.157			
Residual Variance	4.203	2.050				

Note. PC Group = Post COVID group. ICC = intraclass correlation coefficient. For fixed effects linked to a priori directional hypotheses, significance was evaluated using one-tailed p-values, whereas covariates and random intercepts were assessed using two-tailed p-values.

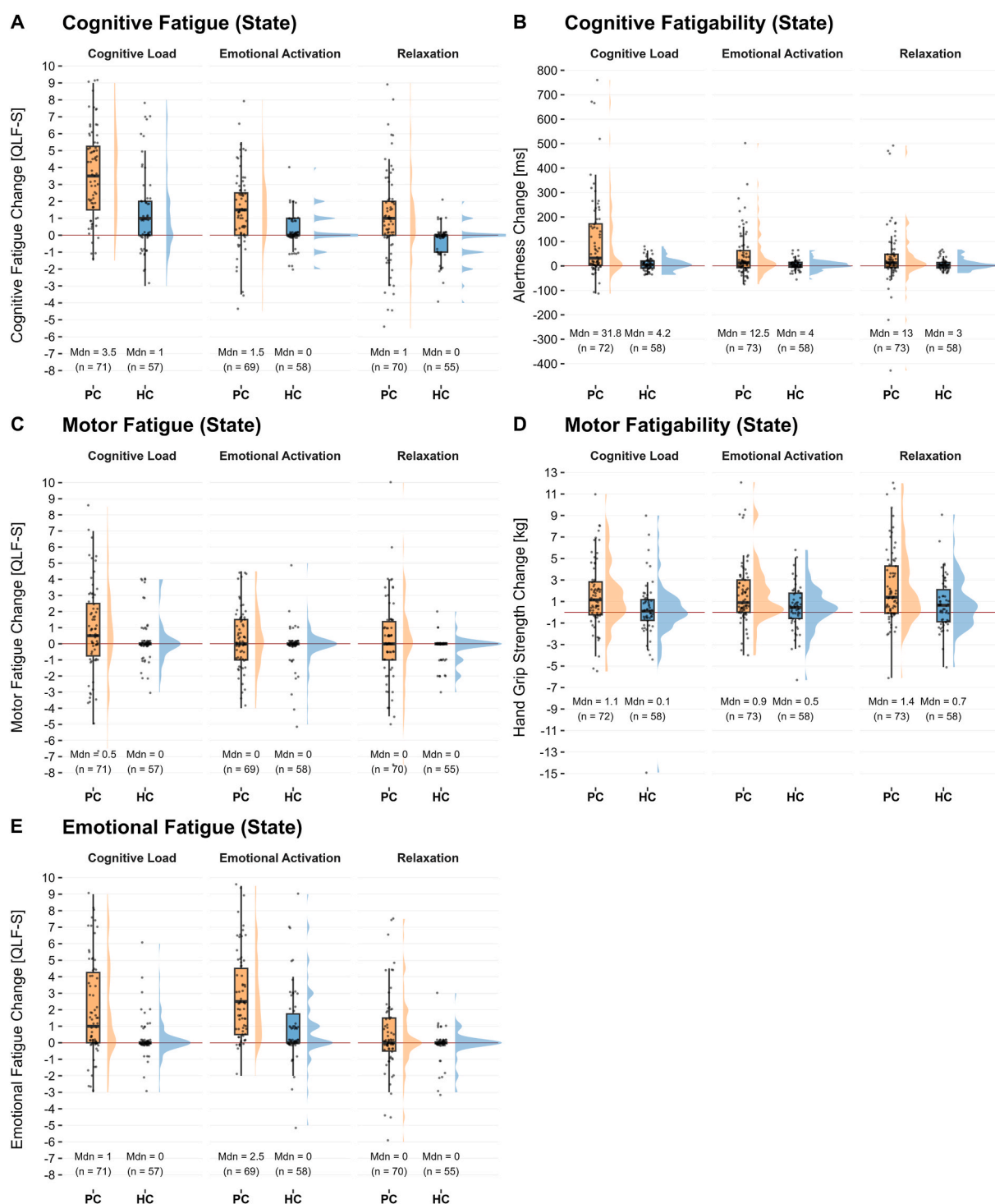


Fig. 4. Pre-to Post-Changes in Fatigue and Fatigability by Group and Load Condition

Note. Raincloud plots on pre-to post-load change scores in alertness [in ms], hand grip strength [in kg], cognitive, motor and emotional Fatigue (QLF-S; Tempfli et al., 2022) by group (PC = post COVID; HC = healthy controls) and load condition. Change scores were computed as post-load minus pre-load values for all variables, except for hand grip strength, where the inverse (pre-load minus post-load) was applied.

healthy controls.

Regarding the co-variables, age and biological sex were significant predictors for emotional Fatigue only, where female sex and higher age predicted higher increase in emotional Fatigue.

4. Discussion

Fatigue is a complex, multifaceted, and debilitating syndrome commonly observed in patients with post COVID. Our multidimensional

assessment aimed to address symptom heterogeneity by examining trait-level, as well as state-level Fatigue and Fatigability following different types of acute load (cognitive, emotional, and relaxation) and comparing these responses between patients with post COVID and healthy controls. We assessed cognitive, emotional, and motor Fatigue using questionnaires, cognitive Fatigability via alertness reaction times and motor Fatigability using hand grip strength. Our key findings include that, with multiple baseline measurements, we could not only show elevated trait Fatigue, reduced alertness, and diminished hand grip strength in the post COVID group, but also high intra-individual variability in the symptoms. Our study design differentiated between Fatigue and Fatigability symptoms across cognitive, motor and emotional domains, making it possible to show state-level interactions specific to the post COVID sample. Importantly, post-COVID patients showed increased cognitive Fatigue and motor Fatigability even after the relaxation condition, indicating heightened vulnerability and suggesting that relaxation exercises shown to be effective in other populations may not translate directly to post-COVID patients. In the following, we will discuss these key findings, starting with the trait level and intra-individual variability, followed by a detailed look at the domain interactions on state-levels.

4.1. Trait levels: higher fatigue, fatigability, and intra-individual variability

4.1.1. Trait Fatigue and Fatigability

Supporting our first hypothesis, patients with post COVID exhibit higher trait Fatigue than healthy controls, with moderate to large effect sizes. Our results do not only reveal a high symptom burden at trait level, which is consistently reported in the current post COVID literature (Atchley-Challenner et al., 2024), but also highlight that this burden affects multiple domains, i.e., cognitive, motor, and emotional. Further, our study demonstrates that the burden not only applies to perceived Fatigue but extends to performance measures. This finding is clinically important because post COVID is often characterized by invisible and fluctuating symptoms, which may contribute to stigma, invalidation, and challenges in the assessment of work ability or disability. Performance-based measures can therefore provide complementary evidence of functional impairment and may help to contextualize patient-reported symptoms without reducing the clinical relevance of subjective experience (Pantelic et al., 2022). Compared to controls, patients with post COVID exhibited significantly higher trait-level cognitive and motor Fatigability, operationalized as prolonged alertness reaction times and lowered hand grip strength across multiple time points. This finding is in line with evidence of reaction-time slowing which points to pervasive attentional inefficiency in post COVID (Hasting et al., 2023; Ortelli et al., 2022). Although only measured at a single time point, Martin et al. (2023) observed reduced tonic alertness in their post COVID sample and linked this impairment to central nervous hypoarousal, indexed by pupillary unrest. Converging evidence for altered central nervous activation also comes from metabolic imaging research. Rudroff et al. (2020) summarized emerging [18F]fluorodeoxyglucose positron emission tomography evidence indicating hypometabolism in several brain regions in post-COVID patients with persistent fatigue-related symptoms. More recent review evidence suggests that regional brain hypometabolism may partly improve over several months in some patients, but often persists and appears to be associated with symptom severity, cognitive impairment, and inflammatory markers (Siqueira et al., 2025). Longitudinal data further indicate that alertness deficits remain unchanged over at least six months and generalize to a wide range of speeded cognitive tasks (Martin et al., 2024), underscoring the persistence and trait-like character of post COVID cognitive Fatigability.

4.1.2. Baseline: intraindividual variability

Post-hoc analyses showed that, for group means, both groups had a

stable baseline of Fatigue and Fatigability across multiple measurement days, with higher levels in post COVID (Table 2, Supplementary Table S4). However, beyond these group-level effects, we observed pronounced intra-individual variability in the post COVID group: many patients showed different baseline Fatigue and Fatigability scores each day. This within-person variability was significantly higher than in the healthy control group. The observed intra-individual variability validates patients' reports of fluctuating symptoms (Wurz et al., 2022), and supports complementing group-level analyses with person-centered approaches to detect differentiated symptom patterns. As a limitation, our variability estimates are based on only three measurements per participant. Nonetheless, they align with evidence highlighting heterogeneity in post-COVID symptoms. Ecological momentary assessment showed that group-level analyses were non-conclusive for fatigue-perpetuating factors in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), whereas individual-level analyses revealed participant-specific strength and even direction of effects (Worm-Smeitink et al., 2021). In post COVID, experience-sampling likewise demonstrated fluctuations in momentary motor and cognitive Fatigue within and across days, some individuals varying more than others (Wensink et al., 2023). This variability highlights challenge for clinical assessments: the fluctuating nature of Fatigue and Fatigability complicates reliable clinical assessment and exposes the limits of single-time-point evaluations, especially in occupational evaluations, where longitudinal assessments are essential.

The comparatively higher Intraclass correlation coefficients (ICC) for alertness relative to Fatigue and hand grip strength may indicate that alertness reflects a more stable between-person characteristic, whereas the other measures capture greater within-person variability across conditions. This interpretation is consistent with the observation that alertness showed less pronounced intraindividual variability at baseline than the Fatigue outcomes. From a mechanistic perspective, this may suggest that alertness, conceptualized as a basal, general wakefulness (Fimm et al., 2023), or its assessment as median reaction time across multiple trials may be less susceptible to contextual and individual influences than self-reported Fatigue measures or hand grip strength. However, these considerations should be treated cautiously, as it is based on descriptive comparisons and a limited number of observations per participant.

4.2. State levels: amplified fatigue and fatigability response after load, and domain interactions

We hypothesized that pre-to post-load changes in Fatigue and Fatigability would differ between groups and across load conditions, which was partly supported by our results. As expected, we found effects of load type on cognitive Fatigue, cognitive Fatigability, and emotional Fatigue, the patient group showing larger changes, i.e. higher state Fatigue and Fatigability. We observed a significant increase of motor Fatigability in the post COVID group, although it was not specific to any load condition. In contrast, our motor Fatigue results did not reveal any significant effects of group or load type. Our results show that healthy controls report increased state Fatigue as a response to acute load. This is an important finding as it indicates that also healthy individuals feel affected by load. Yet, this response is different in the post COVID group. We highlight three aspects in the following.

- (a) As a reaction to load, we only observed significant increases in self-assessed Fatigue but not in Fatigability in healthy controls. In contrast, patients with post COVID did not only show increases in Fatigue, but also in cognitive Fatigability after cognitive load and increased motor Fatigability in response to all load conditions, even the relaxation condition.
- (b) That healthy controls also reported elevated post-load Fatigue raises critical questions about differentiating normative from pathological symptoms. Patients with post COVID must be able to

identify risk states, e.g. leading to Post-Exertional Malaise (Hartle et al., 2021), yet excessive vigilance or catastrophizing can amplify symptoms (Delgado-Sanchez et al., 2023). Emerging therapeutic frameworks address this balance (Tempfli and Randerath, 2025). With individualized diagnostics, clinicians can normalize typical Fatigue and Fatigability and reduce catastrophizing while still validating clinically relevant symptoms. This requires adequate knowledge and symptom classification, supported by comprehensive assessments such as those proposed here.

- (c) Healthy controls responded with Fatigue congruent to the load type: cognitive Fatigue after cognitive load and emotional Fatigue after emotional load. In contrast, patients with post COVID showed interactions across cognitive, emotional, and motor domains. Therapeutically, these interactions suggest that reducing symptoms in one domain (e.g., cognitive or emotional) may concurrently ameliorate other domains or overall fatigue, potentially unveiling novel treatment targets. Accordingly, cognitive behavioral therapy programs targeting multiple fatigue domains simultaneously report improvements across all of them (e.g., Schilling et al., 2023). This cross-domain perspective also suggests that physical training interventions (e.g., Morrow et al., 2022) may affect Fatigue and Fatigability beyond the motor domain, potentially influencing cognitive and emotional symptoms as well. Consistently, preliminary rehabilitation evidence suggests that combined physical and cognitive dual-task training improves cognitive outcomes in post COVID (Deodato et al., 2024).

4.3. State motor fatigue and fatigability

We observed no load-specific effects in the motor domain. Motor Fatigue showed no significant patterns across conditions, which is notable given the pronounced trait-level group differences in motor Fatigue and motor Fatigability. One possible explanation is that the single motor item of the *Questionnaire on Perceived Load and Fatigue – State* (QLF-S) (Tempfli et al., 2025) was not sufficiently sensitive to detect short-term fluctuations in motor Fatigue, or that motor Fatigue was more difficult for patients to identify and rate than cognitive or emotional Fatigue. In addition, state motor Fatigue may be more strongly influenced by external factors, such as varying levels of activity and rest during the clinical routine, whereas the impact of our experimental load conditions may have been comparatively small. Notably, none of the load conditions specifically targeted the motor domain. Future studies should therefore examine whether the QLF-S motor item is sensitive enough to capture acute motor Fatigue fluctuations and should include motor-specific load conditions.

For motor Fatigability, hand grip strength decreased in the post-COVID group but not differentially by load. Methodologically, this questions hand grip strength's specificity and sensitivity as a state marker, declines may index overall physical status rather than acute load responsiveness. Consistently, hand grip strength showed the smallest intra-individual baseline variability of all measures (Fig. 3, Supplementary Table S4), and has been linked to greater symptom severity and disability in post COVID, particularly in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (Paffrath et al., 2024). The non-specific decrease in hand grip strength may reflect heightened general bodily sensitivity to diverse stressors, including demanding aspects of our relaxation condition. Thus, the observed decrease in hand grip strength may reflect either trait-like motor Fatigability, that is, a relatively stable vulnerability to any load-related impairment, or an additional state-dependent Fatigability response elicited by a specific load condition. This distinction cannot be resolved with the present design. Future studies may benefit from repeated assessments and more fine-grained neuromuscular and balance-related outcomes. Electromyography-based protocols may be particularly useful because

they can capture changes in muscle activation during fatiguing contractions, although direct evidence for their sensitivity to acute within-session Fatigability in post COVID remains limited (Almeida et al., 2025). In addition, force-plate-derived measures may provide complementary information on postural control and sensorimotor instability, which have also been shown to be impaired in post COVID (de Sousa et al., 2022).

4.4. Relevance of the emotional domain

Beyond cognitive and motor domains, we incorporated the emotional domain into our multidimensional framework of Fatigue and Fatigability. The post COVID group showed significantly higher trait emotional Fatigue and amplified state emotional Fatigue after emotional activation and cognitive load (but not after relaxation). These findings highlight a substantial emotional symptom burden and support including the emotional domain in research, diagnosis, and treatment.

Further, to our knowledge, this is the first evidence that emotional load contributes substantially to multidomain responses: after emotional activation, emotional Fatigue increased more in patients than in controls; and, in the post COVID group, cognitive Fatigue and motor Fatigability increased in all conditions, including after emotional load. If, as we observed, emotional load perpetuates a systemic fatigue response, reducing it may lower overall symptom severity. As an integral component to a holistic biopsychosocial model, the emotional domain therefore emerges as a therapeutic target. Psychotherapy can be a valuable starting point in this context, and we advocate recognizing psychotherapy as a beneficial, complementary component within holistic care, rather than as competing with or invalidating biological mechanisms (Lemogne et al., 2023). However, emotional activation during therapy may temporarily exacerbate symptoms, which should be carefully considered in therapy planning.

4.5. Potential fatiguing relaxation tasks in post COVID

The relaxation was intended as a control condition with low load intensity. Accordingly, the healthy control group showed no significant increases, but even reductions in cognitive and emotional Fatigue. This is in line with the findings of Gaertner and colleagues showing subjective and physiological relaxation in healthy controls and persons with borderline personality disorder (Gaertner et al., 2024, 2025). However, the relaxation condition unexpectedly increased cognitive Fatigue and motor Fatigability in patients with post COVID. This finding suggests that relaxation may not be inherently restorative in post COVID. One explanation is that physiological and psychological relaxation mechanisms may be less accessible in this population. Paced breathing at approximately six breaths per minute is assumed to promote parasympathetic activity through vagal and baroreflex pathways, while calming nature exposure may reduce arousal through perceived safety and positive affect. However, post COVID is frequently associated with autonomic dysregulation, reduced HRV, sympathetic predominance, impaired vagal and baroreflex function, and POTS (Fedorowski et al., 2024), which may attenuate these mechanisms. In addition, interoceptive hypersensitivity may cause breathing-focused interventions to increase bodily monitoring, breathlessness, or distress despite normal physiological parameters (von Werder et al., 2025).

Another explanation is that the relaxation session itself may not have been low-load for patients. Paced breathing requires sustained attention and respiratory coordination, while virtual reality may cause dizziness or cybersickness, which appear to be increased in post-COVID populations (Llana et al., 2025). Beyond the task itself, the broader study context, including getting to the appointment, social interaction, upright posture, sustained attention, and an approximately 80-min session, may have exceeded patients' regulatory capacity, particularly in those with dysautonomia or POTS (Yong et al., 2023). Taken together, in post COVID, there may be no genuinely low-load condition by default.

Relaxation-based diagnostic or therapeutic procedures may need to be individualized to match autonomic, sensory, cognitive, and interoceptive demands to individual capacities rather than assuming that relaxation exercises are inherently restorative.

4.6. Limitations

The results of this study should be viewed in light of several limitations. The post-COVID sample was recruited from a neurological rehabilitation clinic and therefore represents a clinically selected group. Accordingly, findings may primarily generalize to patients with clinically significant symptom burden limiting everyday functioning and/or work capacity, who are nevertheless sufficiently resilient to participate in inpatient rehabilitation. In contrast, individuals with milder post-COVID symptoms or limited access to specialized medical care are likely underrepresented. At the same time, the study does not represent the most severely affected patients with severe ME/CFS symptoms. This concern is further supported by the high dropout rate, as 32 of 132 eligible patients discontinued participation due to reduced exertion tolerance. Thus, comprehensive diagnostic procedures, particularly when conducted alongside a regular rehabilitation schedule, may not be feasible for all patients across the severity spectrum. This further underlines the need for feasible screening approaches that help identify which patients are likely to benefit from comprehensive assessment and for whom the potential burden and risk of adverse effects related to exertion intolerance may outweigh its diagnostic value. In addition, healthy controls were recruited from university-affiliated databases and therefore constitute a convenience sample. Although the age difference between groups was not statistically significant, the mean age gap of four years may still be clinically relevant given the age sensitivity of performance-based outcomes. Future studies should therefore include more diverse community-dwelling post-COVID samples, including mildly and severely affected individuals, as well as closely matched control groups.

Virus variant distribution differed significantly between groups and may therefore represent a potential confound. However, variant assignment was based on self-reported timing of the first SARS-CoV-2 infection, limiting interpretability due to changes in testing availability, testing behavior, and potential recall bias across the pandemic. Earlier infections may have been underdetected, particularly in healthy controls with mild or asymptomatic courses, whereas infections followed by persistent post-COVID symptoms may have been more salient for patients to recall. Similarly, post-exertional malaise (PEM)-positive status was not included as a covariate in the state-level models, although post-exertional malaise (PEM) is mechanistically central to reactions to load. To avoid exceeding the structural limits of the statistical models, we refrained from adding further covariates and prioritized robust estimation of the primary effects relevant to the study's main focus. Moreover, PEM-positive status was highly prevalent in the patient group (87.7%), supporting the clinical characterization of the sample as highly burdened but providing insufficient variance for reliable estimation of PEM-specific effects. Future studies with larger and more heterogeneous samples should examine whether virus variant and PEM status moderate state-level Fatigue and Fatigability responses.

4.7. Summary and conclusion

Overall, the key challenge in Fatigue and Fatigability research remains the considerable heterogeneity in symptom presentation. Our study contributes to addressing this issue by offering novel insights into symptom dynamics in patients with post COVID. We added evidence to existing research showing that patients with post COVID experience significantly elevated cognitive, motor, and emotional symptom burdens at both trait and state levels compared to healthy controls even after relaxation tasks. Extending previous findings by comprehensively assessing reactions to acute load, we showed that only the post COVID

group exhibited measurable declines in performance in response to acute load in addition to increases in subjectively experienced Fatigue. Furthermore, our findings underscore the relevance of incorporating the emotional domain into a multidimensional Fatigue and Fatigability framework. Differentiating between cognitive, motor, and emotional domains enabled us to demonstrate that while healthy controls showed load-congruent Fatigue increases, patients with post COVID displayed pronounced interactions across these domains in Fatigue and Fatigability measures. Additionally, by including multiple baseline measurements in our study design, we documented substantial intra-individual variability among patients.

In broader context, our results indicate generalized vulnerability and reduced resilience to stressors in patients with post COVID. The observed multidomain interactions suggest systemic overload and may reflect shared pathophysiological mechanisms across Fatigue and Fatigability domains. To substantiate this, future work should address physiological and biomedical pathways. Current literature points to shared pathophysiological factors, including neuroimmune processes, inflammation, hypothalamic–pituitary–adrenal axis dysregulation, and autonomic dysfunction, that likely underlie the multidimensional nature and interactions across Fatigue and Fatigability observed in our study (Al-Hakeim et al., 2023; Davis et al., 2023; Klinkhammer et al., 2024).

Taken together, our results are in line with the approach of a biopsychosocial model for understanding and treating post COVID Fatigue and Fatigability, advocating for multimodal and interdisciplinary approaches. To account for the complexity of Fatigue and Fatigability symptoms, diagnostic processes should expand beyond isolated primary outcomes by incorporating comprehensive multidomain assessments. Future research should focus on individualized multimodal strategies addressing biological, psychological, and social factors to enhance knowledge on individual cross-domain interactions and thereby further disentangle the multifaceted construct of Fatigue and Fatigability.

Ethical statement

All participants gave written consent prior to participating in this study. All procedures were approved by the Ethics Committee of the University of Konstanz (approval no 40/2021) and conducted in accordance with the Declaration of Helsinki.

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CRediT authorship contribution statement

M. Tempfli: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **R.J. Gaertner:** Investigation, Methodology, Writing – review & editing. **C. Mlynski:** Investigation, Resources, Writing – review & editing. **M.S. Gözl:** Data curation, Writing – review & editing. **L. Altfreder:** Investigation, Writing – review & editing. **S. Detzner:** Investigation, Writing – review & editing. **L. Greis:** Investigation, Writing – review & editing. **S. Schwefinger:** Investigation, Writing – review & editing. **S. Weber:** Investigation, Writing – review & editing. **J. Weis:** Investigation, Writing – review & editing. **D. Meindl:** Investigation, Writing – review & editing. **L.H.O. Roth:** Investigation, Writing – review & editing. **M. Fischer:** Investigation, Writing – review & editing. **P.H. Wirtz:** Resources, Writing – review & editing. **V. Job:** Resources, Writing – review & editing. **J.C. Pruessner:** Resources, Writing – review & editing. **C. Weich:** Methodology, Writing – review & editing. **C. Dettmers:** Conceptualization, Methodology, Resources, Writing – review & editing. **M. Jöbges:** Conceptualization, Methodology, Resources, Writing – review & editing. **J. Randerath:** Conceptualization, Funding acquisition,

Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.socscimed.2026.119633>.

Data availability

All code and data analysed in this study are included in this published article's Supplementary Information files.

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