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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The relationship between the psychophysiological stress response and daily functioning in post-COVID-19 syndrome patients

Sil Luyten
Bjorn Swennen

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Katleen BOGAERTS

COPROMOTOR :
dr. Stef FEIJEN

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Research Context

This master's thesis is situated within the ongoing research titled "Cognitive, psychological, and physical functioning in post-COVID-19 syndrome patients with different levels of fatigue" led by our supervisor, Dr. Stef Feijen. Our research falls within the domain of pain, fatigue, and somatically unexplained physical symptoms. The aim of our study is to investigate the relationship between the psychophysiological stress response and the daily functioning of post-COVID-19 syndrome patients.

The project is identified by the Clinical Trials Identifier NCT05758558 and has been approved by the Committee for Medical Ethics at Hasselt University with code CME2022/021 and by the Ethics Committee Research UZ/KULeuven with code S66200.

The COVID-19 pandemic, which occurred from 2020 to 2022, has garnered global attention. Given its significance, extensive research has been conducted on this topic. Published studies primarily focus on diagnosing COVID-19 and its associated symptoms during the acute phase of infection. However, there is limited knowledge about post-COVID-19 syndrome. It remains unclear why some individuals develop post-COVID-19 syndrome symptoms while others do not, and how best to manage them.

This research endeavors to contribute to a better understanding of the complex aftermath of COVID-19 and the development of targeted interventions to improve the quality of life of affected individuals.

As master's students, we have contributed to a research project led by Dr. Stef Feijen and utilized data from this project to address our research question. Every aspect of the master's thesis was discussed with Dr. Stef Feijen. We would like to express our gratitude to Dr. Stef Feijen for his guidance, expertise, and motivation throughout the process of this master's thesis. We would also like to thank Hasselt University for providing us with this opportunity. Furthermore, we extend our appreciation to our supervisor, Prof. Dr. Katleen Bogaerts. Finally, in writing this duo master's thesis, both students have made equal and substantial contributions.

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1 Abstract

Background: The COVID-19 pandemic has caused various physical and cognitive symptoms, with some individuals experiencing persistent symptoms that limit daily life and can lead to post-COVID-19 syndrome.

Objective: This study aimed to investigate the relationship between the psychophysiological stress response and the daily functioning of post-COVID-19 syndrome patients.

Methods: Participants completed demographic surveys, the Fatigue Severity Scale (FSS), and a Baseline COVID questionnaire assessing COVID-related symptoms. The Post-COVID-19 Functional Status scale (PCFS) was utilized to assess daily functioning. Three stress tasks were administered, measuring heart rate (HR) and galvanic skin response (SC). Heart Rate Variability (HRV) data was analyzed from electrocardiogram HR measurements. The Montreal Cognitive Assessment (MoCA) evaluated general cognitive symptoms. A multiple logistic regression model was constructed using the scientifically and statistically significant variables. Data analysis was conducted using the software program JMP.

Results: 30 participants were categorized as "high impairment" (n=25) or "low impairment" (n=5) PCFS. Baseline HRV low frequency (HRV LF_bl, $p < .001$) and high frequency (HRV HF_bl, $p < .001$) significantly predicted daily functioning. High fatigue score (FSS, $p < .001$) and dizziness as post-COVID-19 syndrome symptoms ($p = .004$) were significantly associated with higher functional impairments. No significant psychophysiological changes were observed during stress tasks or recovery phases.

Conclusion: There is no significant relationship between the psychophysiological stress response and daily functioning in post-COVID-19 syndrome patients, though a trend suggests a potential association.

Keywords: Post-COVID-19 syndrome, Post-COVID-19 Functional Status scale, Fatigue Severity Scale, Stress tasks, Psychophysiological stress response, Heart rate variability, Skin conductance

2 Introduction

SARS-CoV-2, a positive-sense, enveloped single-stranded RNA virus, causes COVID-19 and was first reported in Wuhan, China, in December 2019. The World Health Organization (2020) Director-General proclaimed the COVID-19 outbreak a pandemic on March 11, 2020. According to the World Health Organization (WHO), a total of 775 379 864 individuals have been infected with the SARS-CoV-2 virus (WHO, 2024). Approximately 10-20% of those infected with SARS-CoV-2 develop post-COVID-19 syndrome (WHO, 2023).

Many individuals, both hospitalized and non-hospitalized, continue to experience persistent symptoms after initial infection. In 2021, post-COVID-19 syndrome had been defined as the persistence of pre-existing or new symptoms occurring three months after the initial SARS-CoV-2 infection, with these symptoms persisting for at least two months without any other explanation. These symptoms typically have an impact on daily life (WHO, 2021). Being female, having poor pre-pandemic mental health, and having poor overall health were associated with a higher risk of post-COVID-19 syndrome (Thompson et al., 2021).

Reported symptoms of post-COVID-19 syndrome are very diverse, with a significant impact on the individual’s health and quality of life. Fatigue, headache and cognitive impairment, commonly referred to as 'brain fog,' are prevalent symptoms observed in individuals recovering from post-COVID-19 syndrome. Physical exertion, stress, and dehydration have been identified as the primary triggers for these cognitive symptoms (Tabacof et al., 2022). Significantly more than half of post-COVID-19 syndrome patients indicated moderate to severe restrictions in their capacity to perform daily tasks; of these, 38% reported severe limitations in their capacity to work, and 33% reported moderate to severe levels of anxiety or depression (Mahony et al., 2022). According to Mahony et al. (2022), the most frequent complaint was exhaustion or low energy. Many people also reported eating and sleeping irregularities, difficulty concentrating, anxiety, and decreased interest in activities. Unfortunately, 17% of the patients reported having suicidal or self-harming thoughts at least once in the previous two weeks.

The psychophysiological stress response is used in quantifying an individual's reactions under stress and during recovery (Thayer et al., 2012). The psychophysiological stress response is often measured using heart rate variability (HRV) and skin conductance (SC), which are reliable indicators of emotional responses, such as stress. HRV offers indirect evaluations of both sympathetic and parasympathetic cardiac autonomic activity, while electrodermal activity reflects the activity of the sympathetic nervous system (Bhoja et al., 2020). Associations have been identified linking occupational stress with a reduction in HRV (Järvelin-Pasanen et al., 2018). According to Tolin et al. (2021), individuals with social anxiety disorder exhibit increased reactivity in heart rate (HR) and skin conductance response (SCR) compared to those without the disorder, suggesting heightened immediate arousal in response to stressors. Additionally, anxious individuals demonstrated a reduced high-frequency heart rate variability (HF-HRV) response to stressors compared to healthy controls. Moreover, demographic factors also influence HRV. Research demonstrates that age and gender have an influence on HRV. More specifically, aging decreases the HRV. (Koskinen et al., 2009; Gerritsen et al., 2003). In a healthy population, the utilization of a less maladaptive coping strategy can be associated with the ability to keep the HRV at a baseline level when facing a psychosocial stress test. This could suggest that individuals employing an adaptive coping strategy possibly exhibit a more optimal regulation of the autonomic nervous system (A. V. Machado et al., 2021).

Post-COVID-19 syndrome patients often experience significant limitations in daily functioning. Previous research has linked stress with symptoms and limitations in daily functioning in fibromyalgia patients. It demonstrates an association between stress and increased pain, emotional fatigue, and challenges in engaging in self-care behaviors such as adhering to a healthy diet, maintaining regular exercise, or establishing connections with a supportive social network when experiencing stress (Waichler, 2023). However, the relationship between functioning and the psychophysiological stress response in post-COVID-19 syndrome patients remains poorly understood (Mahony et al., 2022). Consequently, our goal is to investigate the relationship between the psychophysiological stress response and daily functioning in post-COVID-19 syndrome patients, as we observed a correlation between HRV and daily life in fibromyalgia patients (Cohen et al., 2000). This, in turn, may facilitate more targeted research and treatment endeavors in the future for post-COVID-19 syndrome patients. In our research, we hypothesize that patients with low impairments in functioning (PCFS grades 0-1-2) will exhibit lower skin conductance and greater heart rate variability compared to patients with greater limitations in functioning (PCFS grades 3-4).

3 Methods

3.1 Design

This cross-sectional study was based on the larger study investigating "Cognitive, Psychological and Physical Functioning in PCS-patients with different levels of fatigue". Approval for this study was obtained from the Ethics Committee Research UZ/KULeuven and the Committee for Medical Ethics of Hasselt University (B3222022000817).

3.2 Participants

Within the larger study, flyers were distributed at nearby specialized private practices, written media (local newspapers), and private social media groups targeted for post-COVID-19 syndrome (Facebook, Langdurige klachten na COVID in Vlaanderen) during the recruitment process. Anyone who was interested in participating after COVID-19 would have had instant access to an online information document that outlined the requirements for inclusion in the study as well as the procedures that followed. After that, those who would like to take part could email the research team. Once the participant consented to participate in the study, two measurement sessions were scheduled.

3.2.1 Inclusion criteria

The recently published definition of the post-COVID-19 syndrome condition served as the basis for the inclusion criteria for study participation (WHO, 2021). Post-COVID-19 syndrome is defined as an illness that affects people who have been confirmed to have had SARS-CoV-2 infection. Symptoms usually appear three months after COVID-19 first appears, last for at least two months, and cannot be attributed to an alternative diagnosis. Although it was not required, participants were encouraged to submit their test certificate.

Furthermore, participants were required to report current persistent symptoms, such as brain fog, shortness of breath, headaches, and others, and indicate on the post-COVID-19 Functional Status Scale that these symptoms had an impact on their daily functioning. These symptoms could reappear following the initial recuperation from the acute COVID-19 episode or they could continue after the initial sickness, but they had to last for more than two months. Patients also needed to report experiencing significant levels of fatigue at that moment. The Fatigue Severity Scale (FSS) was used to measure the degree of fatigue (Krupp et al., 1989). The validated Dutch version was used to prevent language-related barriers (Rietberg et al., 2010). For practical reasons (insufficient number of participants), we did not exclude patients diagnosed with another condition from the study. In future studies, this is something to take into consideration.

Additional inclusion criteria were as follows:

- Age over 18 years old.
- Willing to sign the digital informed consent.
- Able to speak and comprehend Dutch.
- Must have tested positive for COVID-19, confirmed by either reverse transcription polymerase chain reaction (RT-PCR), computed tomography (CT) of the lungs, or a symptom-based diagnosis by a general practitioner.

3.3 Procedure

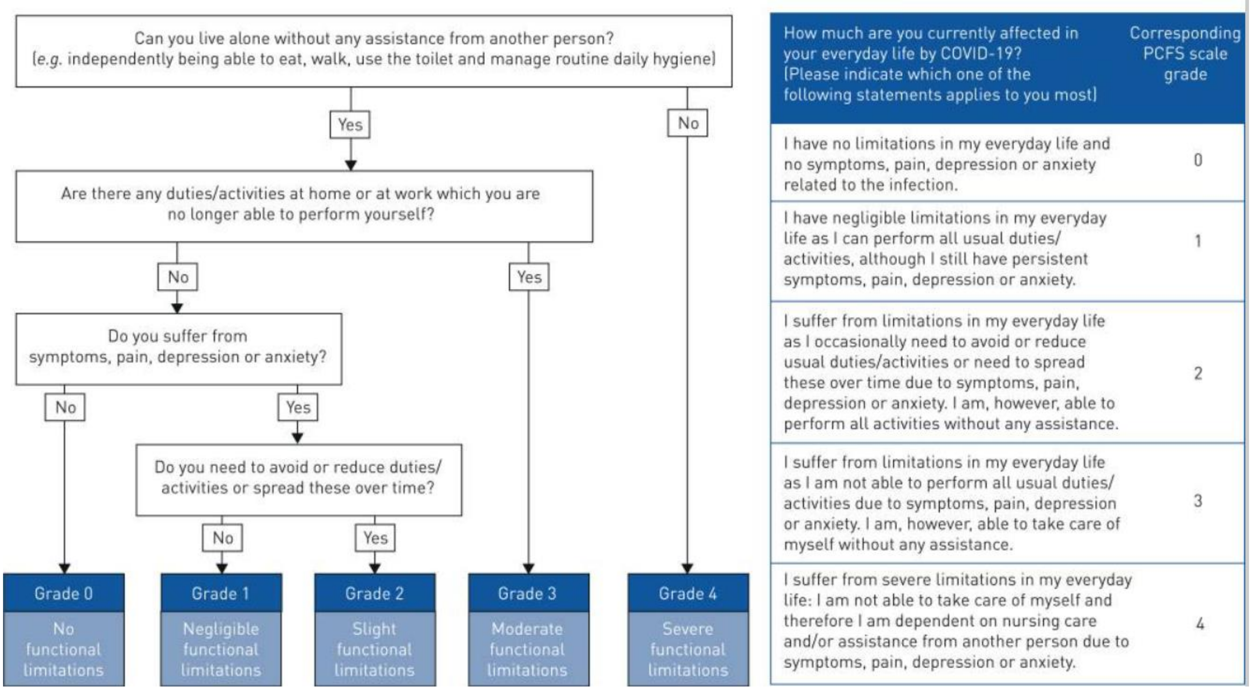
Participants meeting the pre-defined inclusion criteria were eligible to proceed with further participation in the study. These participants were invited to two separate testing sessions to assess their cognitive, physical and psychological functioning. Participants were asked to sign an informed consent form prior to any measurements. Next, participants were asked to complete a digital or paper-based baseline questionnaire regarding demographics (gender and age) and fatigue. If they scored higher than 36 on the FSS, they were identified as individuals experiencing fatigue (Krupp et al., 1989). The participants were also required to complete a Baseline COVID questionnaire, which enabled us to assess COVID-related symptoms (muscle pain, dizziness, elevated resting heart rate, concentration difficulties, sleep problems, comorbidities, headache and anxiety). Additionally, a comprehensive post-COVID Functional Status assessment was required. The Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the body height in meters. Cognitive functioning was evaluated using the Montreal Cognitive Assessment (MoCA), a tool designed to assess general cognitive impairment across multiple domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation (Julayanont & Nasreddine, 2017). A score below 26 on the MoCA indicates cognitive impairment (Nasreddine et al., 2005).

3.3.1 Post-COVID-19 Daily functioning

The Post-COVID-19 Functional Status scale had been used as a measurement instrument in this study. The PCFS is a self-report measure that allows us to track how the illness was affecting daily functioning. The PCFS consisted of four questions that allowed the participants to be categorized into five groups (Leite et al., 2022). According to Leite et al. (2022), the people in PCFS grades 3–4 showed higher levels of fatigue symptoms, lower health related quality of life (HRQoL), and inferior functional performance when compared to those in PCFS grade 0. Furthermore, those with PCFS grades 1-2 demonstrated lower HRQoL compared to PCFS grade 0 participants, and higher functional performance compared to PCFS grade 3–4 individuals. The PCFS was recently validated by F. V. C. Machado et al. (2021).

Figure 1

The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19



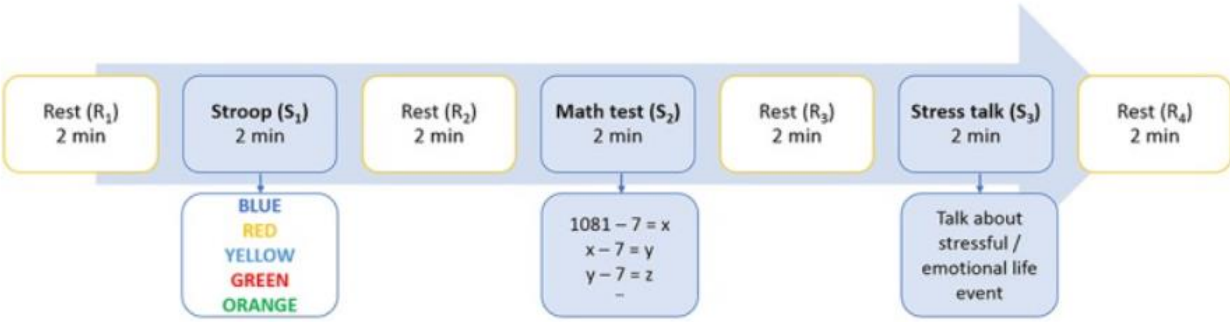
Note. In this figure, the five scales of the PCFS are explained. Adapted from Klok et al. (2020).

3.3.2 Stress response on three stress tasks

The patients with post-COVID-19 syndrome went through a stress test comprising three stress tasks, with a total duration of approximately 15 minutes. Following these three stress-inducing tasks, there was a two-minute recuperation period. The first stressor to be administered was the Stroop color-word task (Van Der Elst et al., 2006), which lasted for two minutes. During this task, participants were shown a list of words, each representing a color name. However, the color of the ink in which the word was written did not always match the color name that the word represented. For example, the word "red" might be written in blue ink. The participants' task was to name the color of the ink in which the word was written, rather than reading the word itself. The second stressor was a mathematical exercise where the person had to deduct seven from a predetermined amount (1081). To induce additional stress, the experimenter intervened by saying "wrong" or "faster" during the first 2 tasks. This task also lasted for two minutes. A stress talk was the last and third source of stress (Liao & Carey, 2015). The participant in this task had to talk nonstop for two minutes about a recent stressful event, detailing their feelings and ideas at the time. The timeline of the experiment is shown in Figure 2.

Figure 2

The Timeline of the Experiment



Note: R1 ,R2 and R3 = rest periods ; S1, S2 and S1 = stress tasks (Smets et al., 2018).

3.4 Measurements

To record the physiological response of the individual to the stressors, we recorded the participant's heart rate, skin conductance and breathing pattern continuously during the stress protocol. The only goal of these stressors was to cause a physiological reaction. To measure the respiratory rate, we placed one sensor just below the belly button and one sensor high on the thorax. Skin conductance was measured at 32 Hz. The electrodes were placed as distally as possible on the distal phalanx of the non-dominant hand. To measure heart rate, we used the electrocardiogram signal. This was measured by placing electrodes on the left and right just below the clavicle and on the left just below the lowest rib. This physiological response was evaluated using the Nexus-10 MKII device, which allowed us to measure a wide range of physiological parameters. According to Selvaraj et al. (2008), this device has been shown to generate reliable data. The data we recorded would then be processed using Bio Trace+ software (Mind Media BV). Through this device, we were able to obtain HRV data derived from heart rate measurements. HRV was assessed using frequency domain analysis, a method that provides detailed insights into autonomic regulation and is particularly suited for short-term measurements. HRV_LF is regarded as an indicator of both sympathetic and parasympathetic activity, whereas HRV_HF primarily reflects parasympathetic activity. The HRV_LF/HF ratio is utilized to evaluate the balance between sympathetic and parasympathetic activity (Shaffer & Ginsberg, 2017). Additionally a baseline measurement for these variables was conducted prior to the stress tasks.

3.5 Data analysis

Analyses were conducted using data from 30 participants who completed the protocol. BMI data was missing for one participant due to dropout. One participant did not complete the Baseline COVID questionnaire. Analyses using the scores of the questionnaire were performed with data from 29 participants. Two other participants did not complete the MoCa test for cognitive symptoms. Psychophysiological data from the stress tests was available for all 30 participants. Due to the small number of participants in each PCFS category, the participants were divided into two groups for the PCFS: (low impairment) grade 0-1-2 (negligible or mild functional limitations), which accounted for 16.67% of all participants, and (high impairment) grade 3-4 (moderate to severe functional impairments), which accounted for 83.33% of all participants. These two PCFS groups were compared during the three stress tasks. The statistical software program JMP17 was used for the data analysis, which was carried out in two phases. Throughout all analyses, the primary outcome measure was the PCFS score, labeled categorically as ‘high impairment’ or ‘low impairment’. Descriptive statistics were used to characterize the sample. We used frequency for categorical variables, means and standard deviations (SD) for normally distributed continuous data, and median and interquartile ranges for non normally distributed continuous data.

In the first phase, psychophysiological variables were assessed for their relevance as dependent variables in the model using simple logistic regression to analyze the effects of HRV and SC. HRV averages, calculated only for rest periods due to the influence of verbal activities (Bernardi et al., 2000), included HRV_Low Frequency (HRV_LF), HRV_High Frequency (HRV_HF), HRV_baseline (HRV LF_bl, HRV HF_bl, HRV LF/HF_bl), and HRV_Low Frequency/High Frequency (HRV_LF/HF). SC averages were calculated for rest (SC R1, R2, and R3) and stress periods (SC S1, S2, and S3), as well as baseline SC (SC_bl). Variables were selected for the final model based on a p-value threshold of less than 0.20.

Post-COVID-19 syndrome symptoms were analysed, including cognitive symptoms (measured by the MoCA), fatigue (measured by the FSS), muscle pain, dizziness, elevated resting heart rate, concentration difficulties, sleep problems, comorbidities, headache, and anxiety (measured by a baseline COVID questionnaire). Furthermore, we also analysed three demographic variables: age, gender and body mass index (BMI). Again, variables with a p-value less than 0.20 were considered for inclusion in the final model.

In the second phase, the selected variables were integrated into a single model. First, the psychophysiological variables were added to the model, followed by the clinical symptoms. This model was refined using stepwise regression, and its adequacy was assessed using the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AICc) values. The most suitable model was used for interpreting the results. Alternatively, we executed the same procedure but reversed the order of variable inclusion: first incorporating the clinical symptoms, followed by the psychophysiological variables.

4 Results

A total of 30 participants were recruited for this study. Table 1 provides an overview of the demographic characteristics.

Table 1

Characteristics of the participants

	High impairment	Low impairment
Age (Years)	48.16 ± 8.84	47.80 ± 12.38
BMI (KG/m²)	26.01± 5.40	27.84 ± 5.92
Female	17	1
Male	8	4
MoCA	28 (26 – 29)[c]	29 (27 – 29)[c]
FSS	54 (51.5 - 59)[c]	41 ± 11.58[d]
Muscle pain[b]	84%	100%
Dizziness[b]	44%	20%
Elevated resting heart rate[b]	40%	40%
Concentration difficulties[b]	60%	20%
Sleep problems[b]	52%	20%
Comorbidities[a,b]	48%	80%
Headache[b]	60%	40%
Anxiety[b]	24%	0%

Note. BMI = Body Mass Index; High impairment = grade 3 or 4 of the PCFS scale; Low impairment = grade 0, 1 or 2 of the PCFS scale; MoCA = Montreal Cognitive Assessment; FSS = Fatigue Severity Scale

[a]The subgroup "comorbidities" comprises diabetes, lung disease, heart disease, kidney disease, anxiety disorder, depression, hypertension, obesity, rheumatism, Parkinson's disease, stroke, osteoporosis, migraine, burn-out, chronic fatigue syndrome, chronic pain, dementia, thrombosis, peripheral vascular disease, multiple sclerosis, fibromyalgia, neck and/or back pain, liver disease, and contact dermatitis. [b]Were obtained through the Baseline COVID Questionnaire. [c]Is the median. [d]Is the mean

4.1 Psychophysiological Stress Response

The primary outcome measure used is the PCFS category. Five participants were labelled as 'low impairment' and 25 as 'high impairment'. As shown in Table 2, none of the psychophysiological variables were statistically significant during the stress tasks or during the recovery phases between the stress tasks. Figure 3 and 4 illustrate a trend suggesting a potential association between a lower PCFS score and a lower average HRV (LF/HF) as well as a lower HRV (LF/HF) at baseline. Figure 5 and 6 show that skin conductance appears to be lower during stress measurements as well as during rest periods in the PCFS group 'low' compared to the PCFS group 'high'. The same result is evident in Figure 7 during the baseline skin conductance measurement. However, these relationships lack statistical significance. The remaining variables did not demonstrate any significant association or trend.

Table 2

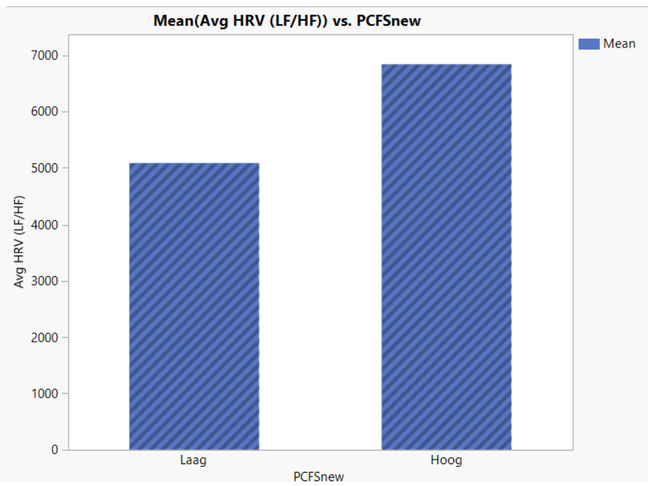
Psychophysiological Stress Response

Psychophysiological stress variable	*p*
Avg HRV LF	0.799
Avg HRV (LF/HF)	0.475
Avg HRV HF	0.485
Avg SC S1, 2, 3	0.421
Avg SC R1, 2, 3	0.396

Note. Avg HRV LF = Average Heart Rate Variability Low Frequency; Avg HRV (LF/HF) = Average Heart Rate Variability (Low Frequency/High Frequency); Avg HRV HF = Average Heart Rate Variability High Frequency; Avg SC S1, 2, 3 = Average Skin Conductance in Stress tasks 1, 2 and 3; Avg SC R1, 2, 3 = Average Skin Conductance in Rest periods 1, 2 and 3.

Figure 3

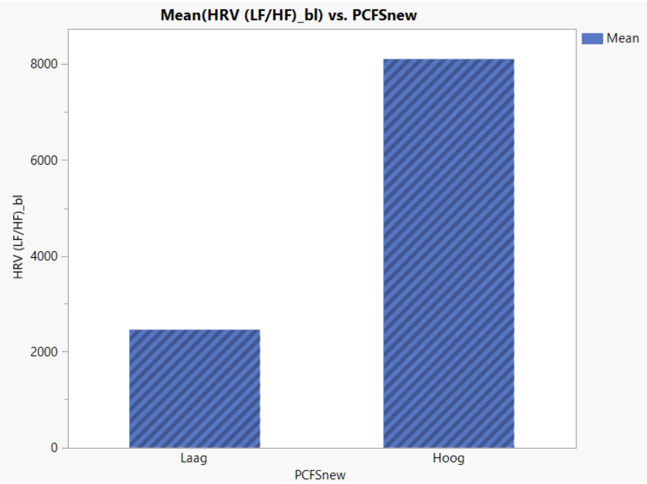
Comparison of Mean Average HRV (LF/HF) between PCFS groups



Note. Avg HRV (LF/HF) = Average heart rate variability (low frequency/high frequency); PCFS = Post-COVID-19 Functional Status scale; PCFS score 0, 1 or 2 = ‘low’; PCFS score 3 or 4 = ‘high’

Figure 4

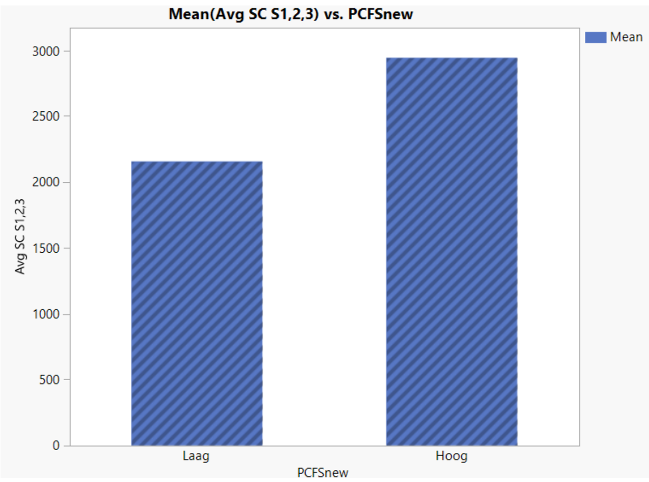
Comparison of Mean HRV (LF/HF) at Baseline between PCFS groups



Note. HRV (LF/HF)_bl = Heart rate variability (low frequency/high frequency) at baseline; PCFS = Post-COVID-19 Functional Status scale; PCFS score 0, 1 or 2 = ‘low’; PCFS score 3 or 4 = ‘high’

Figure 5

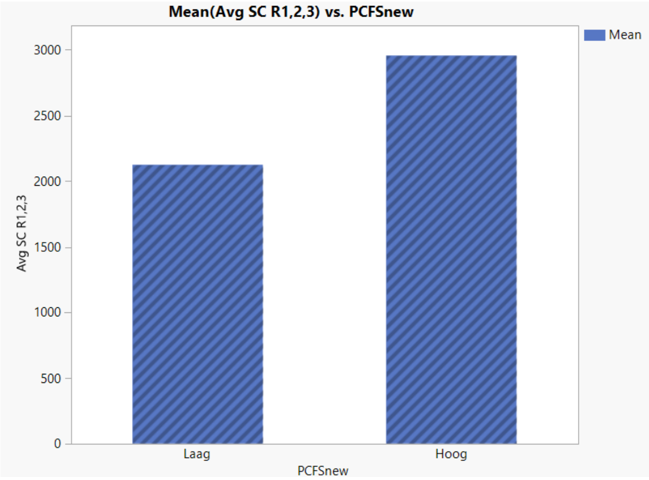
Comparison of Mean Avg SC during stress tasks between PCFS groups



Note. Avg SC S1,2,3 = Average skin conductance during stress tasks 1,2 and 3; PCFS = Post-COVID-19 Functional Status scale; PCFS score 0, 1 or 2 = ‘low’; PCFS score 3 or 4 = ‘high’

Figure 6

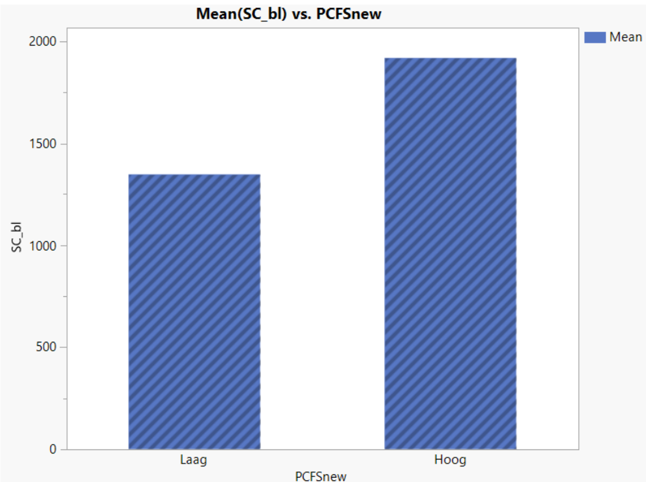
Comparison of Mean Avg SC during rest periods between PCFS groups



Note. Avg SC R1,2,3 = Average skin conductance during rest periods 1,2 and 3; PCFS = Post-COVID-19 Functional Status scale; PCFS score 0, 1 or 2 = 'low'; PCFS score 3 or 4 = 'high'

Figure 7

Comparison of Mean SC at Baseline between PCFS groups



Note. SC_bl = Skin conductance at baseline; PCFS = Post-COVID-19 Functional Status scale; PCFS score 0, 1 or 2 = 'low'; PCFS score 3 or 4 = 'high'

4.2 Key Predictors for Identifying the PCFS Scale

After establishing the model with the best fit, multiple logistic regression indicated that the following variables were the strongest predictors of the model: HRV LF_bl ($p < .001$; *OR*, 1.009), HRV HF_bl ($p = .001$; *OR*, 1.014), FSS ($p < .001$; *OR*, 2166.619), post_symptoms dizziness ($p =$

0.004). These variables are presented in Table 3. There were no significant interactions between these predictors. The Akaike Information Criterion (AICc) value was 12.609. The Bayesian Information Criterion (BIC) value was 16.837. The following assumptions were checked: multicollinearity and independence. The variables in the final model had VIF values ranging from 1 to 5, indicating a low to moderate degree of multicollinearity. All measurements were independent; no paired measurements were taken, and none of the participants were related to each other.

Table 3

Key predictors for Identifying the PCFS Scale

	OR	**Estimate**	***p***
HRV LF_bl	1.01	0.009	< .001*
HRV HF_bl	1.01	0.014	.001*
FSS	2166.62	7.68	< .001*
Post_symptoms dizziness		-43.62	.004*

Note. HRV LF_bl = Heart Rate Variability Low Frequency at baseline; HRV HF_bl = Heart Rate Variability High Frequency at baseline; FSS = Fatigue Severity Scale
*p < 0.05

5 Discussion

The primary objective of our study was to investigate how the psychophysiological response to stress and subsequent recovery contributes to daily functioning outcomes in individuals with post-COVID-19 syndrome. The psychophysiological stress response was assessed utilizing three stress tasks, while daily functioning was measured employing the PCFS scale. Contrary to our initial hypothesis, the findings of this investigation did not substantiate a statistically significant relationship between psychophysiological stress response and daily functioning in post-COVID-19 syndrome patients. A potential explanation may lie in the time frame of both the stress task and the recovery task, each lasting only 2 minutes. It is possible that differences become more apparent after a longer period. Another explanation for these findings could be the heterogeneity between the two groups and the small sample size or low number of participants in the ‘low impairment’ group. This was an initial exploration that examined the relationship. Further studies and analyses may yield more concrete results.

5.1 Exploration of the findings

Regarding the measured psychophysiological variables during stress and rest periods, no significant relationship was observed with the PCFS categories. Nonetheless, the data suggest a potential association, indicating that lower average HRV (LF/HF), lower baseline HRV (LF/HF), and lower skin conductance during baseline, stress tasks, and rest may be associated with a lower PCFS category. This could be explained by the assumption that a higher LF/HF ratio indicates a dominance of the sympathetic nervous system. During a stressful event, the sympathetic nervous system will get activated through a fight-or-flight response or a parasympathetic inhibition (Shaffer & Ginsberg, 2017). Increased sympathetic activity could thus indicate that these individuals experience more stress or encounter more stressful situations (Ziegler, 2012), perhaps due to the numerous limitations in their daily functioning. This could also explain why participants in the high impairment category exhibit higher skin conductance, as they have increased activity of the sympathetic nervous system, since according to Iwase et al. (1997), excessive sweating is caused by overstimulation of the sympathetic nervous system. More perceived stress can again be linked to daily functioning in the context of fatigue (Kocalevent et al., 2011).

In our study, we identified a significant relationship between baseline heart rate variability (HRV) measurements (HRV LF_bl and HRV HF_bl) and the PCFS categories. Interestingly, we did not find any previous studies that examined this relationship between baseline HRV and daily functioning in post-COVID-19 syndrome patients. Because many post-COVID-19 syndrome symptoms overlap with those of COPD and fibromyalgia, we can compare with the connection between baseline HRV and daily functioning in COPD patients (Komaroff & Lipkin, 2023). According to Van Gestel et al. (2011), HRV is independently associated with quality of life in patients with COPD. We also investigated the association of HRV in fibromyalgia patients, and from the study by Cohen et al. (2000) we observed a correlation between HRV parameters and physical function, quality of life, psychological well-being, depression, overall health, and physical pain in fibromyalgia patients. From this, we infer that HRV in fibromyalgia patients influences daily functioning. Therefore, HRV could serve as a crucial marker for monitoring and enhancing daily functioning in patients with post-COVID-19 syndrome.

Our findings highlight the significant role of dizziness and fatigue in explaining poorer daily functioning. The FSS demonstrated a significant relationship with functional status, which is consistent with the results reported by Leite et al. (2022), who showed that individuals in PCFS grades 3-4 exhibited higher levels of fatigue symptoms compared to those in PCFS grade 0. This aligns with earlier research that found fatigue to be a dominant symptom among individuals with post-COVID-19 syndrome and that it impacts their daily functioning (Walker et al., 2023). In this study, they used the Work and Social Adjustment Scale (WSAS) to identify the patient's functional limitations. We observed a similar relationship in other conditions, such as COPD. Kouijzer et al. (2018) demonstrated that fatigue has a severe, negative impact on the physical, emotional, cognitive, and social functioning of participants. These limitations in daily functioning negatively influence the quality of life of patients and impose a significant mental burden, diminishing patients' joy in life. Therefore, we emphasize the importance of the need for treatments targeting fatigue. It is also crucial to increase awareness among healthcare professionals and patients about the existing impact of fatigue on daily life. Moreover, previous research suggests a significant relationship between dizziness and disability, affecting various aspects of daily functioning such as mobility, work, self-care, and communication (Rodríguez-Pérez et al., 2022). Thus, addressing dizziness and fatigue should be prioritized in the treatment of patients with post-COVID-19 syndrome to potentially improve their daily functioning.

Lastly, our study found no significant relationship between the PCFS category and demographic characteristics. This contrasts with the findings of Rodríguez-Pérez et al. (2022), who reported a significant influence of age on functioning and dependency levels. Gender, however, did not influence functioning, consistent with our results. These unequal results regarding age can possibly be explained by the significantly larger sample size of the study by Rodríguez-Pérez et al. (2022).

5.2 Strengths and limitations

To our knowledge, this is the first study investigating the relationship between psychophysiological data of the stress response protocol and daily functioning in post-COVID-19 syndrome patients. A wide range of variables was investigated on the basis of previous research in similar conditions. Furthermore, there was a low dropout rate, thereby resulting in minimal missing data that could potentially influence the outcomes. All measurements were standardized in their conduct. The sequence, location, and the individual conducting the measurements remained consistent throughout. The utilized scales and questionnaires have been validated in prior research. The inclusion were carefully selected, aligning with the definition of post-COVID-19 syndrome provided by the WHO.

This study has several limitations that must be addressed. Firstly, the small sample size and the cross-sectional design constrain the generalizability of the findings and hinder the ability to establish causal relationships. Additionally, the uneven distribution of participants in PCFS categories one and two (16.67% vs 83.33%) may introduce bias into the results, potentially skewing the representation of outcomes. Furthermore, the stress tasks utilized may not have effectively captured the daily stressors encountered by post-COVID-19 syndrome patients, potentially attenuating the observed associations between stress reactivity and daily functioning. Furthermore, we did not exclude individuals with another similar condition, which means that the results could equally be attributed to this other condition.

Another limitation arises from the use of subjective questionnaires, which rely on participants' memory recall and subjective interpretation on their experience. Memory recall biases and the reconstructive nature of memory processes may influence the accuracy of reported symptoms, potentially affecting the reliability of the data collected.

Moreover, the day-to-day fluctuations in symptoms experienced by patients could contribute to variability in test performance and results. Addressing strategies to mitigate the impact of these fluctuations on data consistency and reliability in future studies is essential.

Finally, because post-COVID-19 syndrome is a recent phenomenon, there are few studies on the relationship between psychophysiological variables and post-COVID-19 syndrome. This makes it difficult to contextualize the findings, although comparisons have been made with COPD and fibromyalgia.

5.3 Implications and recommendations for further research

Longitudinal studies with larger cohorts are required to validate these findings and to clarify the direction of the observed relationships. In future research, it appears more appropriate to conduct measurements during periods of stress occurring in daily life rather than in a laboratory setting, as daily life presents different stress-inducing factors. This is because a laboratory environment may not adequately simulate the daily stressors that post-COVID-19 syndrome patients experience. Future studies could potentially involve participants who have no other conditions besides post-COVID-19 syndrome, in order to exclusively analyze the impact of post-COVID-19 syndrome.

We can utilize these findings to develop a more targeted approach towards addressing the symptoms that adversely affect the daily functioning of post-COVID-19 syndrome patients.

6 Conclusion

Our study did not reveal a significant relationship between the psychophysiological stress response, measured by average HRV and SC during stress tasks and rest periods, and daily functioning in post-COVID-19 syndrome patients. However, we do observe a trend between these variables, which may indicate a potential association between the psychophysiological stress response and daily functioning. We also found that baseline HRV measurements were significantly linked to the functional status of patients, suggesting that lower autonomic flexibility is correlated with greater functional impairments. Furthermore, symptoms such as dizziness and fatigue emerged as strong predictors of poorer daily functioning among post-COVID-19 syndrome patients.

7 References

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8 Appendices