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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

An experimental study investigating the link between symptom reporting and heart rate variability in chronic fatigue syndrome patients

**Jentro Dest
Daan Grosemans**

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

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We would like to thank everyone who helped us during the intensive period of preparing our thesis: “An experimental study investigating the link between symptom reporting and heart rate variability in chronic fatigue syndrome patients”.

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We are grateful to the patients and participants who contributed with their time and energy to our research. Their openness and assistance were critical in acquiring the data we needed for our investigation.

Lastly, we would like to express our gratitude to the University of Hasselt for providing the tools and atmosphere that enabled us to conduct our study. We are also thankful to UZ Leuven for allowing us to use their research facilities and equipment for our study. This research would not have been achieved without their assistance. We hope that our findings will aid in the growth of knowledge in this sector and lead to further research.

Research context

Our Master's thesis falls within the research domain of Rehabilitation Sciences and Physiotherapy. In our study we investigated patients with chronic fatigue syndrome (CFS). CFS is a complicated disorder of which the pathology is still poorly understood. Due to the significant prevalence, the socio-economic impact of the disorder is high. In addition to the physiological dysfunctions that are often reported in CFS literature, patients can also experience altered symptom perception. Patients for example show increased subjective responses to unpleasant somatic stimuli in comparison with healthy persons (Van den Houte et al., 2018). Therefore, this study project fits within the domain of pain, fatigue and somatically unexplained physical symptoms. Despite a lot of articles reporting the role of altered symptom perception, they mainly focused on symptom perception in the lab. However, these laboratory measurements do not take day-to-day variability in symptoms into account. We think that the lack of studies investigating the symptomatology in CFS patients via ecological momentary measurements is a gap in the literature. Therefore, in our study, we executed symptom assessments in the lab and in daily life. In addition, we investigated the interactions between the reported symptoms and heart rate variability (HRV) in order to investigate, on a small scale, if psychological and physiological dysfunctions in patients do not work independently. Extra information about the pathology of CFS is useful to all professionals in rehabilitation sciences and physical therapy who work with CFS patients. It will help professionals to understand the complex problem of CFS better and to tailor the care for these patients.

Our study is situated in a larger study project with the title "Identifying (psycho)physiology-based subgroups in chronic fatigue syndrome and their relevance for rehabilitation" and with study number S66452. The project is reimbursed by Fonds Wetenschappelijk Onderzoek. The project runs in collaboration with the Multidisciplinary Diagnostic Center of UZ Leuven, the Multidisciplinary Expertise Center Tumi Therapeutics, the Vlaams Instituut voor Biotechnologie KU Leuven Raes Lab and IMEC. All laboratory tasks were conducted in the University Hospital of Leuven.

The study is written in line with the central format. The study topics and research questions were determined in collaboration with Msc. Y. Dooms and Dr. Maaïke Van Den Houte. Due to the fact that the study was a component of an ongoing research project, we were not involved in decisions about research design or methodology. We carried out the academic writing procedure concerning this Master's thesis. During the writing procedure, we received input from Msc. Y. Dooms. The thesis was written in close cooperation amongst both of us. We both independently contributed to the thesis, reviewed it, and wrote multiple sections together. The data-analysis was done in collaboration with Dr. Maaïke Van Den Houte.

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1. Abstract

Background: Chronic fatigue syndrome (CFS) is characterized by chronic physical and cognitive fatigue. Studies showed that psychological and physiological dysfunctions can play a role in its pathology.

Objectives: This study aimed to explore the altered symptom perception and autonomic nervous system dysfunction in patients via laboratory and daily life measurements

Methods: We included five CFS patients and seven healthy controls (HC). We assessed daily life symptoms via experience sampling method. In the laboratory, we assessed fatigue via the Fatigue and energy scale, stress via a visual analogue scale and heart rate variability (HRV). We performed all measurements in rest and in an exercise condition.

Results: This study found that CFS patients had higher resting heart rate (HR) and reduced heart rate variability (HRV) during activity. Before and after exercise, there was a negative correlation between HRV and mental loss of energy (LOE) and cognitive function. CFS patients experienced increased mental LOE and physical fatigue at rest and following exercise. Prior to and after laboratory tests, they had heightened general physical fatigue, mental LOE, physical LOE, and cognitive function loss.

Conclusion: This study emphasizes the interaction between psychological and physiological components while revealing the complicated CFS symptomatology in their daily life and during laboratory testing. Understanding the complex interactions between symptoms and HRV offers new perspectives on the complex nature of CFS, which could lead to better diagnosis and treatment strategies.

Keywords: Chronic fatigue syndrome (CFS), laboratory, real-life, Heart rate variability (HRV), fatigue, stress.

2. Introduction

Chronic fatigue syndrome (CFS) is a complicated chronic condition. Until now, the pathophysiology of CFS remains poorly understood and no one has been able to identify diagnostic biomarkers yet. Therefore, CFS patients are diagnosed via symptom-based criteria. The literature contains several diagnostic criteria. The 1994 Centers for Disease Control and Prevention Fukuda criteria are the ones most commonly used. They describe CFS as a debilitating illness characterized by chronic cognitive and physical fatigue that lasts for more than six months and results in limitations in daily activities. Besides this, four or more of the following symptoms should be present simultaneously: impaired memory or concentration, glandular swelling in the neck or axilla, sore throat, diffuse myofascial pain, multi joint pain, new type of headache, non-refreshing sleep and post-exertional malaise (PEM) (Fukuda, 1994). Patients with CFS can suffer from a wide variety of symptoms. CFS is related to physical, psychological, and social discomfort, making this 'functional somatic syndrome' biopsychosocial in nature (Yeomans & Conway, 1991). Previous studies report several physiological dysfunctions that can play a role in the pathology of CFS. Several studies show increased levels of pro-inflammatory cytokines in CFS patients (Sandler & Lloyd, 2020; NICE, 2021). In addition, CFS research shows alterations in brain structure and function and neuroinflammation in patients (Maksoud et al, 2020; M. E. Robinson et al, 2016). Third, some studies observed a different composition of the gut microbiota in CFS patients (Lupo et al., 2021; König et al., 2022). In addition, there are some assumptions concerning altered levels of short-chain fatty acids (SCFA) in CFS patients. All these pathophysiological characteristics are related to certain clinical characteristics like swollen lymph nodes due to immunological changes (Montoya et al., 2017). These symptoms are often very comparable to typical CFS symptoms. Many studies, investigating CFS patients, even reported significant links between the pathophysiological results and traits characteristic of chronic fatigue syndrome/symptoms like memory loss, cognitive dysfunction, reduced activity and cognitive and physical fatigue (Miller et al., 2014; Mackay & Tate, 2018; Morris et al., 2015; Lupo et al., 2021; König et al., 2022). Another system that is often reported in the CFS literature is the stress-response systems (SRS). During stress, the autonomic nervous system (ANS) initiates the fight-or-flight response. To keep the sympathetic system active, the slower hypothalamic pituitary adrenal (HPA) axis reacts by releasing cortisol in the blood. Results prove that both

systems can play a role in the pathophysiology of CFS (Crofford, 1998; Gur & Oktayoglu, 2008). Despite inconsistent results, researchers observed altered cortisol levels in CFS patients compared to healthy participants (Van Den Eede et al., 2007; Cantor, 2005; Papadopoulos & Cleare, 2012; Montoya et al., 2017). In addition, there exist evidence that these altered cortisol levels correlate with sleep disturbances, attentional problems, fatigue and pain severity (Torres-Harding et al., 2008; Adam et al., 2006; Nijhof et al., 2014; Deumer et al., 2021; Lai et al., 2020). The heart rate variability (HRV) is an objective, non-invasive way to investigate ANS functioning. According to the literature, patients with CFS tend to have lower HRV, corresponding with sympathetic overactivity and/or parasympathetic underactivity (Parker et al., 2001). However, studies are still inconclusive about this result. Many researchers mainly focused on HRV during rest and several CFS studies reported associations between rest HRV and symptoms like fatigue severity (Escorihuela et al, 2020).

Van den Houte et al. (2018) found that patients with CFS can experience psychological dysfunctions characterized by altered symptom perception due to the compromised interaction between the bottom-up and top-down regulation of afferent physiological signals. However, previous studies focused on laboratory measurements lacking ecological validity and retrospective questionnaires with recall bias. Via Experience Sampling Methodology (ESM) it is possible to explore symptomatology in natural settings. As a result, they make it possible to explore parameters that are variable in daily life and difficult to control in lab settings (Weber et al., 2022). There is a lack of studies investigating the symptom assessment in CFS patients during their daily life. In addition, the link between symptom assessments in the lab and in daily life is unclear. Therefore, in our study, we compared symptomatology measurements in the lab with ecologically-valid measurements. We did this in CFS patients as well as healthy persons. Secondly, there is a lack of research investigating the link between symptom perception and physiological dysfunctions in CFS. An attempt has been made in the ANS literature reporting associations between HRV and CFS-related symptoms. However, these studies mainly focused on HRV during rest. Therefore, we investigated if the HRV in rest differs from the HRV during a cognitive challenge. In addition, the link between HRV during the challenge and feelings of cognitive fatigue was examined. These measurements were performed in CFS and healthy subjects.

3. Methods

3.1 Participants

Five CFS patients (45.20 ± 15.48 years old, five women) and seven healthy controls (46.29 ± 12.79 years old, five women) took part in our study. We recruited people with CFS via the Multidisciplinary Diagnostic Center (MDC) of the University Hospitals from Leuven, which is the only MDC for CFS accredited by the Belgian National Institute for Health and Invalidity Insurance. To be included in the CFS group, the participants had to be diagnosed with CFS in accordance with the 1994 Centre of Disease Control and Prevention Fukuda criteria (Fukuda et al., 1994) after a thorough evaluation by internists and psychiatrists with expertise in fatigue assessments. These criteria include a debilitating illness characterized by chronic cognitive and physical fatigue that lasts for more than six months and results in limitations in daily activities. Besides this, four or more of the following symptoms should be present simultaneously: impaired memory or concentration, glandular swelling in the neck or axilla, sore throat, diffuse myofascial pain, multi joint pain, new type of headache, non-refreshing sleep and post-exertional malaise (PEM). A healthy control group was matched based on age, sex, body mass index and level of education. They did not fulfill the diagnostic criteria. Participants did not participate in another clinical interventional study one month prior to the screening visit and throughout the study. Next, they had a stable intake of medication one month prior to the start of the study, they also did not take any medication influencing stress physiological characteristics (e.g. corticoids, beta blockers, opiates, other anti-inflammatory treatments) and they did not take any antibiotics three months or less prior to the baseline visit. Furthermore, all participants did not have a previous history of drug or alcohol abuse and were not pregnant or lactating during the study period. Finally, subjects from both groups did not have other severe medical illness(es) such as malignancy, severe heart disease, kidney disease or neurological diseases. Additionally, the healthy participants did not have any psychiatric disorders. All the participants were native Dutch speakers.

3.2 Experimental tasks

We performed measurements in both controlled laboratory settings and in real life settings in order to acquire a comprehensive and accurate result of these systems.

3.3 Laboratory variables of psychophysiology in chronic fatigue syndrome

3.3.1 Maastricht Acute Stress Test (MAST)

We used the MAST to execute measurements of stress in the laboratory. The MAST is a validated task that induces a strong physiological and subjective stress response and does not significantly show signs of habituation or sensitization after multiple administrations (Smeets et al., 2012; Quaedflieg et al., 2017). On the day of the test, participants refrained from caffeine, strenuous physical exertion, brushing their teeth, chewing gum and smoking. In addition, participants did not consume alcohol from 24 hours before the MAST and did not drink anything else than non-sparkling water from one hour before the MAST.

The MAST started with a five-minute preparation phase during which we explained the task to the participants (Smeets et al., 2012). Then, a ten minute stress-inducing phase started (Quaedflieg et al., 2017; Smeets et al., 2012). During this phase, subjects alternatively performed a mental arithmetic task and a hand immersion task. The mental arithmetic task consists of counting aloud backwards from 2043 in steps of 17 as quickly and precisely as possible. Each time the participant would make an error, he or she received negative feedback and was instructed to restart at their previous correctly stated answer. During the hand immersion task, participants needed to immerse their left hand in cold water of 6°C. Participants were not told how many trials there would be. They were informed that the computer would select the length of the two different trials randomly and that the duration would vary between 45 and 90 seconds. However, in reality, the order and duration of the trials was fixed. Five hand immersion trials (HI) and four mental arithmetic trials (MA) were alternated in the following sequence and length (Figure 1): HI (90 s), MA (45 s), HI (60 s), MA (60 s), HI (90 s), HI (90 s), MA (45 s), HI (60 s). Participants continued with either task until the computer gave them a sign to start with the next task. Participants were also informed

that they would be videotaped in order to evaluate their facial expressions later on and that they had to look into the camera while performing the test.

However, the only reason why this was done was to deceive the subjects in order to add a social stress component. Neither the participants nor the face expressions were ever filmed and analyzed at any point in time. After the stress-induction phase, a 55-minute recovery phase started.

To determine subjective stress responses, participants rated the stressfulness, painfulness, and unpleasantness of the stress induction procedure on a 100 mm visual analogue scale (VAS) with anchor 0 "not at all" and 10 "extremely". The first VAS (VAS 1) was filled out approximately at baseline prior to the stress-induction phase, the second VAS (VAS 2) after the second mental arithmetic task and the final VAS (VAS 3) at the end of the stress-induction phase, after the last Hand immersion trial. Figure 1 gives an overview of the MAST procedure.

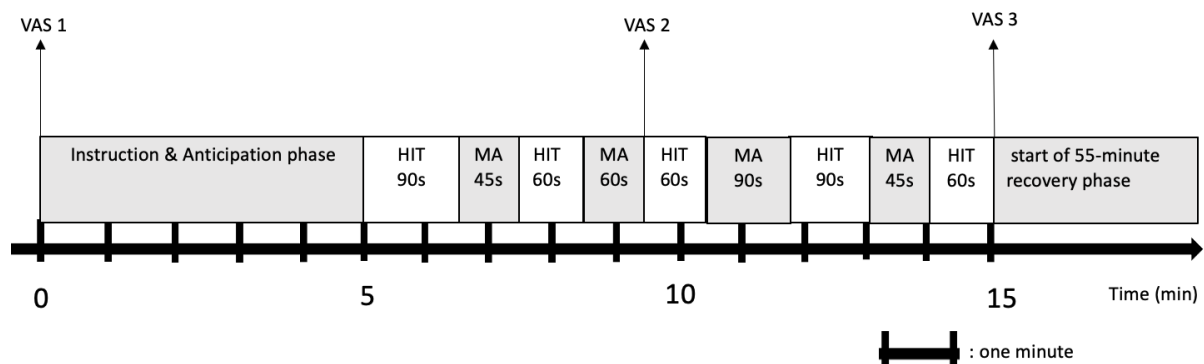


Figure 1. This figure gives an overview of the MAST procedure with visual analogue scale (VAS) measurements. The MAST starts with assessing VAS 1, immediately followed by a five-minute explanation of the task. Afterwards the MAST test itself started, this test lasted for ten minutes and included two alternated tasks: Hand immersion trial (HIT) and mental arithmetic task (MA). VAS 2 is taken after the second mental arithmetic task and VAS 3 at the end of the stress-induction phase. After the test a rest period of 55 min starts, where participants can watch a documentary.

3.3.2 Heart rate variability

To assess the function of the ANS in the laboratory, we measured HRV. The HRV is a measure of the variability in the time between two consecutive heartbeats, the RR-interval. The HRV is quantified as the root mean square of successive differences, which is the major measure of vagal tone in the temporal domain (Shaffer & Ginsberg, 2017). To measure HRV, we used an electrocardiogram (Firstbeat Life Bodyguard 2, Firstbeat Technologies Oy, Finland) and electrodes (Ambu BlueSensor L electrodes, Firstbeat Technologies Oy, Finland). We performed HRV resting-state assessments. For this, subjects sat down in a chair for ten minutes with closed eyes, hands on their thighs and uncrossed legs. In addition, we measured HRV continuously during the paced auditory serial attention task (PASAT). Via the PASAT, we induced a cognitive challenge. The PASAT will be discussed later on in the section of 'cognitive fatigability task'.

3.3.3 Fatigue-inducing tasks

In our study, cognitive and physical fatigability were assessed in the laboratory. We were able to determine these self-reported symptoms, using the Dutch version of the Fatigue and Energy Scale (FES), after participants completed the modified version of the PASAT and an arm-and-leg cycle task, respectively.

3.3.4 Cognitive fatigability task

The modified version of the Paced Auditory Serial Attention Test (PASAT) was used as a laboratory-based assessment to induce cognitive fatigue. The modified version of the PASAT is a test that was previously used in studies investigating mental fatigability in CFS patients (Cook et al., 2007). During this test, participants listened to a computer program reading a series of numbers varying between one and nine. Whenever two consecutive numbers summed up to ten, they had to click on the left mouse button on the keyboard of the computer as fast as possible. The rate at which the numbers appeared was consistent. Numbers appeared for 1500 milliseconds with 500 milliseconds rest between two consecutive numbers. Additionally to this, the computer screen continuously presented

three separate numbers. Each number was only presented for 500 milliseconds after which it was replaced by another number. Therefore, it was too hard to perform any arithmetic task with these numbers. The aim of the visual task was to distract and interfere with the main auditory task. The combination of both tasks increased the complexity and attentional demands and resulted in greater mental fatigue (Cook et al., 2007).

Before starting, participants practiced the task for 30 seconds. Then, when they got used to it, they executed the modified version of the PASAT three times for three minutes with 30 seconds rest between each block. During each block, the program read 120 numbers of which 35% were correct responses. In the rest periods, we emphasized that participants needed to keep focused on the listening as well as the visual task. After three blocks, there was a rest period of fifteen minutes. Figure 2 represents an overview of the PASAT.

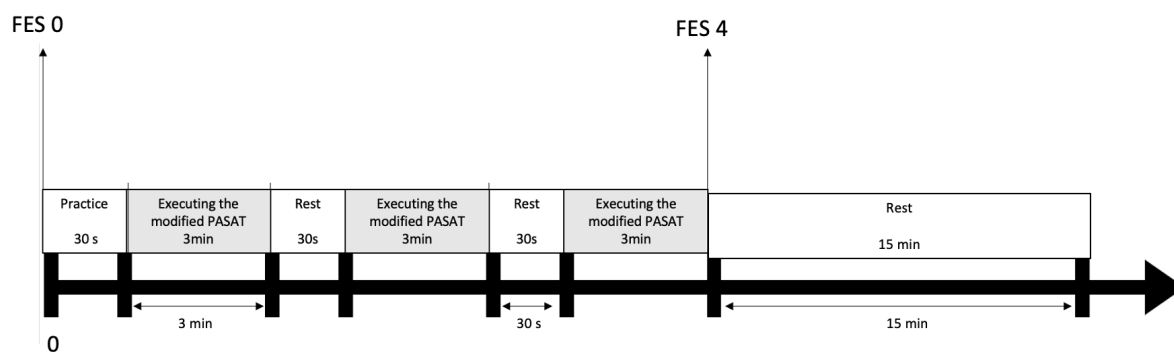


Figure 2. This figure gives an overview of the Paced Auditory Serial Attention Test (PASAT) procedure with Fatigue and Energy Scale (FES) measurements. The PASAT is a cognitive fatigue-inducing assessment test. The test starts with assessing FES 0 followed by a 30 sec practice round. After the practice round FES 1 is filled out followed by a 3 min first trial of the test. After trial 3, FES 4 is filled out followed by fifteen minutes of rest before the next test starts (see physical fatigability task). Used Abbreviations in this figure are: minutes (min),seconds (s).

3.3.5 Physical fatigability task

Physical fatigability was assessed by executing a 25-minute physical cycling task on a combined arm-leg cycle ergometer (Schwinn Air-dyne, Schwinn Fitness, US). The cycling speed was determined by measuring heart rate with a chest strap (Polar T31, Polar, BE). Via Bluetooth, we could connect the chest strap with the ergometer which allowed us to see the

heart rate values while participants were cycling. During the first three minutes of the test, the participants were instructed to increase their cycling tempo until they got feedback from us saying they could maintain that specific cadence for the remainder of the test. Meaning that participants needed to achieve a cycling rate that was in accordance with 70% of their age-predicted maximal heart rate. Similarly to Keech et al. (2015), cycling rate was calculated as $208 - (0,7 * \text{age})$. Participants were unaware of the rate at which they needed to cycle as well as their heart rate during the task. We only gave them feedback to “bike faster” or “bike slower” to make sure that their heart rate remained constant within a range of three beats per minute around the intended heart rate. After completing the physical fatigue task, subjects rested for 30 minutes. In figure 3, we presented an overview of cycling protocol. This task is previously used in CFS patients to increase physical fatigue (Keech et al., 2015; White et al., 2010).

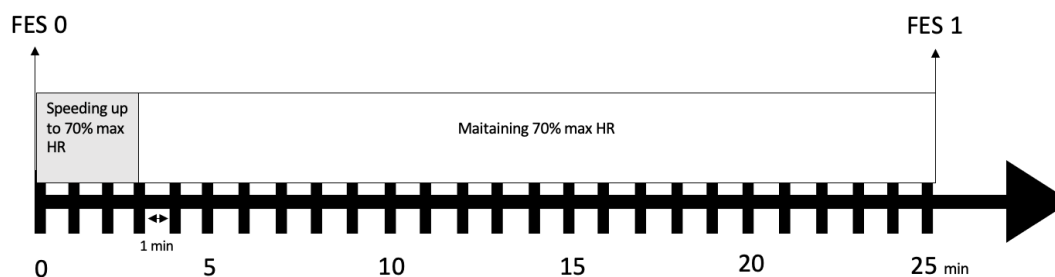


Figure 3. This figure gives an overview of the arm-leg cycle procedure with Fatigue and Energy (FES) measurements. FES 0 was taken before the start of the test, afterwards participants started the test where they were instructed to gradually increase their cycling speed within a range of three beats per minute around the intended heart rate. After the 25 min cycle test, FES 1 was taken.

3.3.6 Fatigue and energy scales

To report physical and cognitive fatigue, subjects filled in a Dutch translation of the Fatigue and Energy scale (FES) (Keech et al; 2015). This is a validated scale developed by Keech et al. (2015) to assess momentary physical and cognitive fatigue in CFS patients. The scale consists of six items divided in a physical and cognitive section, each containing three items and descriptions. Participants rated each item using a 10-point Likert scale with anchors “None” and “Absolute Maximum”. To determine cognitive fatigability, the participants completed the

FES to the instruction phase and immediately after each block of the PASAT. To assess physical fatigability, subjects filled in the FES prior to the task explanation and immediately after the cycling task.

3.4 Real life variables of psychophysiology in chronic fatigue syndrome

The ecological momentary assessment approach, also called ESM, was utilized to assess symptoms experienced by the subjects during their daily life. The ESM is characterized by ad hoc and repeated assessment of a subject's environment and natural state (Weber et al., 2022; De Vries et al., 2021). To determine these outcomes, we downloaded the online app “m-path” on the smartphone of the participants. M-path® is a free app developed by KU Leuven that complies with De General Data Protection Regulation (GDPR) for professionals and their clients who want to continue receiving treatment outside of the therapy session (m-Path – Free tool for blended care by KU Leuven, 2023). The application is copyrighted by KU Leuven R&D, who retains all rights. We lent a smartphone to participants who did not have one.

The participants got push alerts from the M-path app asking them to respond to the prepared questions about their affective state, degree of stress, level of physical, social, and mental activity and level of physical and mental fatigue. **Appendix A** provides a summary of the ESM questions and their answer/score options. The ones used for this thesis are highlighted in yellow. For our study, we mainly focused on the questions assessing physical and cognitive fatigability and stress symptomatology. A slider of 0 = ‘none’ till 10 = ‘absolute maximum’ was used to score the first (sub)question(s) about fatigue, a slider of 0 = ‘not at all’ till 100 = ‘absolute maximum’ was used to score the question about stress, multiple choice answers were used to measure the question about physical activity before the beep and a slider of 0 = ‘not at all’ till 100 = ‘absolute maximum’ was used to score the question about mental activity before the beep. Each of the eight questionnaires that were sent throughout the day contained the exact same questions. Subjects were able to see the precise score they were giving while replying.

The ESM was carried out by the participants over a seven-day period during their daily life. The app sent eight notifications with one identical questionnaire every day within a personally selected window (mean time window: [7:45 -21:10], mean duration: 13.25h). In order to decrease predictability, we preprogrammed the questionnaires using a semi-random sampling scheme. Each question was sent in a fixed time block of one hour. However, the exact moment in each block when the subjects received the questionnaire was determined randomly by the app. The program offered the subjects fifteen minutes to complete the survey following the push notification. After this, the survey expired or was marked incomplete. If subjects did not fill in the questions after five minutes, subjects received a reminder.

3.5 Study procedure

This study was part of a bigger study. The cross-sectional part of the study involved a total of three hospital visits. Between visits one and two, measurements of ESM were taken. At the third visit, stress testing and fatigue assessments were made in the laboratory using the ECG measurements, the MAST, the PASAT and a combined arm-leg cycling task (Figure 4).

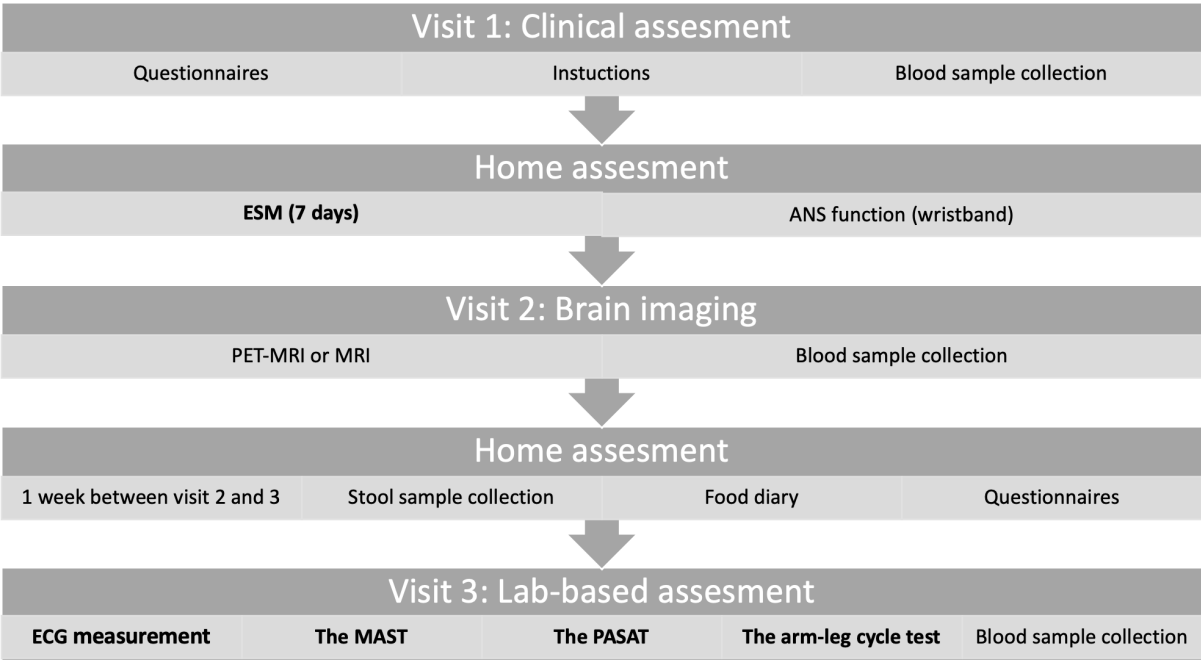


Figure 4. The figure presents an overview of the large clinical experiment of which our Master’s thesis was part of. In our Master’s thesis, we used ESM-data, ECG measurements,

subjective output during the MAST and fatigue-related output during the PASAT and the cycling task, these are also indicated in bold.

3.6 Data analysis

3.6.1 Calculation of the variables

3.6.1.2 Variables obtained in the laboratory

Concerning the physical fatigue task, we used the scores of the FES items “loss of energy” and “general fatigue” obtained immediately prior to the start of the cycling task and immediately after the end of the task to create the four variables: “Physical LOE before the cycle task”, “physical LOE after the cycle task”, “general physical fatigue before the cycle task” and “general physical fatigue after the cycle task”. Likewise, we used the FES scores during baseline and after the third trial to calculate six cognitive fatigue outcomes: “Mental LOE before the PASAT”, “Mental LOE after the PASAT”, “cognitive function before the PASAT”, “cognitive function after the PASAT”, “brain fog before the PASAT” and “cognitive function after the PASAT”. For the stress ratings, we used the scores given by the participants on the stress item of the VAS prior to the start of the MAST and immediately after the end of the MAST to assess the two variables “stress before the Mast” and “Stress after the MAST”.

3.6.1.3 Variables obtained in the daily life

We used the official FES template to determine which experience sampling method (ESM) questions were equivalent to the laboratory FES questions, see **Appendix B**. To assess the physical fatigue levels in the daily life of the subjects, we used the scores of the questions: “op dit moment voel ik mij fysiek uitgeput”, “mijn fysieke energie is” and “op dit moment voel ik me fysiek vermoeid”. For the variable “General physical fatigue daily life”, we averaged the sum of the questions “op dit moment voel ik me fysiek uitgeput” and “op dit moment voel ik me fysiek vermoeid”. We used the scores on the question “mijn fysieke energie is” to create the variable “Physical LOE daily life”. We assessed cognitive fatigue using the scores of the ESM questions “op dit moment ervaar ik mist in mijn hoofd”, “Op dit moment ervaar ik concentratieproblemen”, “Op dit moment voel ik me gedesoriënteerd”, “Op dit moment voel ik me mentaal vermoeid”, “Op dit moment ervaar ik geheugenproblemen” and “Op dit

moment voel ik me mentaal uitgeput". We took the average of the scores on the questions "op dit moment voel ik me mentaal uitgeput" and "op dit moment voel ik me mentaal vermoeid" to create the variable "Mental LOE daily life". Next, the variable "Cognitive function daily life" refers to the average of the scores rated on the questions "op dit moment voel ik me gedesoriënteerd", "op dit moment ervaar ik geheugenproblemen" and "op dit moment ervaar ik concentratieproblemen". The scores of the question "op dit moment ervaar ik mist in mijn hoofd", were used to generate the variable "brain fog daily life", which assessed brain fog. Finally, we created the variable "Stress daily life" by taking into account the scores given on the question "op dit moment voel ik me gestresseerd". We studied the variables "Brain fog daily life", "cognitive function daily life", "Mental LOE daily life", "General physical fatigue daily life" and "Physical LOE daily life" during baseline condition as well as after exercise. We specified the baseline condition as the situation during which subjects scored "no physical activity" and "zero" on the questions "vijf minuten of minder voor de biep afging, voerde ik een fysieke activiteit" and "vijf minuten of minder voor de biep afging, leverde ik een mentale inspanning", assessing physical and cognitive activity, respectively. In contrast, we specified the physical exercise condition as the situation during which participants indicated "moderate physical activity" or "severe physical activity" as a response to a question asking them about physical activity. Similarly to the physical exercise condition, we defined the cognitive exercise condition as the condition during which participants rated the question "vijf minuten of minder voor de biep afging, leverde ik een mentale inspanning" with a score of 50 or higher, corresponding with a moderate to severe mental activity. For the variable "Stress", we defined the exercise condition as the condition in which the subjects indicated to have performed "moderate physical activity" or "severe physical activity" and/or when subjects scored 50 or higher on the question "vijf minuten of minder voor de biep afging, leverde ik een mentale inspanning". For each variable in each condition, we calculated the final score by averaging the scores of each completed corresponding question during the seven days of the ESM measurement. In addition, we also calculated the difference score for each variable in each condition by subtracting the baseline score from the exercise score for each participant.

3.6.2 HRV-data processing

The HRV was determined as the root mean square of successive differences (RMSSD). To calculate the RMSSD, we first assessed the time intervals between each consecutive heartbeat. These are called the R-R intervals or interbeat intervals (IBI). We measured time intervals in seconds. Thereafter, we detected and processed artifacts in IBI-data using the software tool of Artiifact created by Kaufmann et al. (2011) (Matlab, version 2.13, Würzburg, Germany). The processed data can be used for HRV-analysis when the artifacts are replaced by estimated values. To be able to process artifacts, we included data for IBI-analysis between 100s and 700s. Next, median absolute deviation detection was used on the data to detect artifacts. Then, the algorithm processed the data with cubic spline interpolation. The data of one subject needed to be modified so that only data between 50s and 600s were included, because there were too many outliers in close proximity for the software to be able to apply an appropriate artifact. During artifact detection, the interpolation rate of 4Hz, window size of 256s, window overlap of 50%, and frequency bands of 0.04-0.15-0.1 Hz were used.

3.6.2 Statistical data analysis

The software program JMP (Pro 16.2.0, SAS Institute USA) was used to analyze the data for this research. Non-parametric tests were applied due to the limited sample size (five CFS patients and seven healthy subjects).

The difference in fatigue-related and stress symptoms between CFS patients and healthy controls was examined using the Wilcoxon rank sum test. We compared the two groups for the symptoms experienced during daily life and in the lab for the baseline condition as well as for the exercise condition. We also used the Wilcoxon rank sum test to compare the difference scores between both groups in daily life and in the lab.

We investigated if there were any differences between the heart rate (HR) and HRV between the patients and the healthy subjects with the non-parametric Wilcoxon rank sum test. We did this both for the baseline and the cognitive exercise condition. In addition, we again used

the Wilcoxon signed rank test to study differences between HRV in rest and after a mental challenge induced by the PASAT.

We assessed the link between the difference scores of the symptoms experienced by participants in the laboratory and in their daily life. Further, we examined the correlation between HRV measurements at baseline and HRV measurements during the laboratory cognitive exercise condition. Finally, we performed a correlation analysis between the HRV measurements and cognitive CFS-related symptoms “brain fog before the PASAT”, “cognitive function before the PASAT”, “Mental LOE before the PASAT”, “brain fog after the PASAT”, “cognitive function after the PASAT” and “Mental LOE after the PASAT”, all measured in the laboratory. All the correlation analyses were executed with the non-parametric Spearman’s rank-order correlation.

4. Results

4.1 Comparing CFS-related symptoms between CFS patients and HC

4.1.1 CFS-related symptoms at baseline during daily life

We found a significant result for the variables “General physical fatigue daily life “ ($p=0,01$, median= 4.55 with interquartile range (2.74-5.50) for CFS patients and median= 0.97 (0.44-1.49) for HC) and “Mental LOE daily life” ($p=0.03$, median= 2.64 (0.92-4.65) for CFS and median= 0.10 (0-0.39) for HC), indicating that the patients experience higher physical fatigue and a higher mental LOE compared to the patients during their daily life when they did not perform any physical or mental activity. ‘Physical LOE daily life”($p= 0.11$, median= 4.04 (3.25-5.07) for CFS and median= 5.7 (4.68-5.96) for HC); “Brain fog daily life” ($p= 0.15$, median= 0.66(0.11-2.55) CFS and median= 0(0.00-0.02) for HC); “Cognitive function daily life” ($p= 0.14$, median= 0.91(0.08-2.96) CFS and median= 0(0.0-0.03) for HC); “Stress daily life” ($p= 0.47$, median= 5.17(0-29.21) CFS and median= 0(0-0.19) HC) were all not significant. (See figure 5)

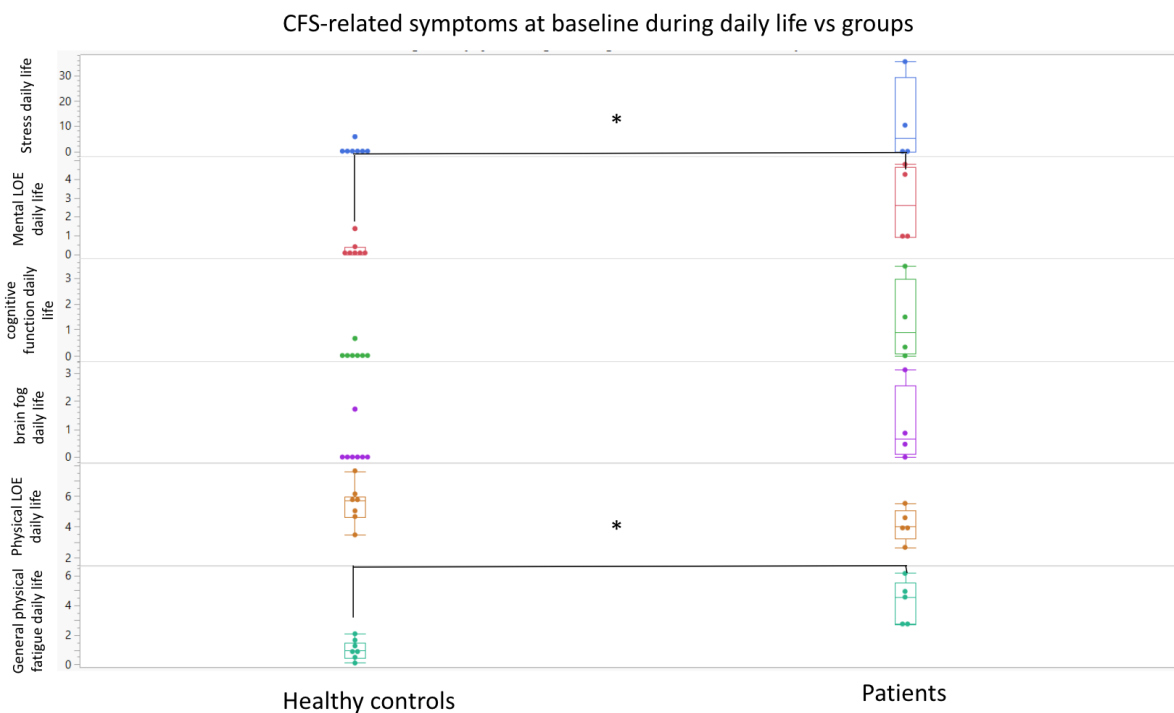


Figure 5. This figure shows the distribution and the difference between healthy controls (HC) and chronic fatigue syndrome patients for experience sampling methodology based variables at baseline for cognitive fatigue, physical fatigue and stress. *= $p < 0.05$, indicating significant results. “General physical fatigue daily life” and “Mental loss of energy (LOE) daily life” were both significant compared with healthy controls.

4.1.2 CFS-related symptoms after exercise during daily life

We found a significant result for the variables “General physical fatigue daily life” ($p = 0.01$, median = 4.00(2.16-6.00) for CFS and median = 0.69 (0.05-1.84) for HC); “Mental LOE daily life” ($p = 0.02$, median = 3.22(1.77-5.81) CFS and median = 0(0-1.06) HC); “Brain fog daily life” ($p = 0.05$, median = 1.29 (0.56-3.50) CFS and median = 0(0-0.36) HC); “Cognitive function daily life” ($p = 0.02$, median = 1.10(0.41-3.09) CFS and median = 0(0-0.21) HC); “Stress daily life” $p = 0.03$, median = 24.08(6.04-28.27) CFS and median = 0.33(0.06-8.56) HC). Indicating that the patients experience higher physical fatigue, a higher mental LOE, more brain fog, more loss of cognitive function and more stress compared to the HC during their daily life when they performed any physical or mental activity. “Physical LOE daily life” ($p = 0.21$, median = 5.5(2.5-6.06) CFS and median = 6.8(5.25-8.00) was not significant. (Figure 6)

CFS-related symptoms after exercise during daily life vs groups

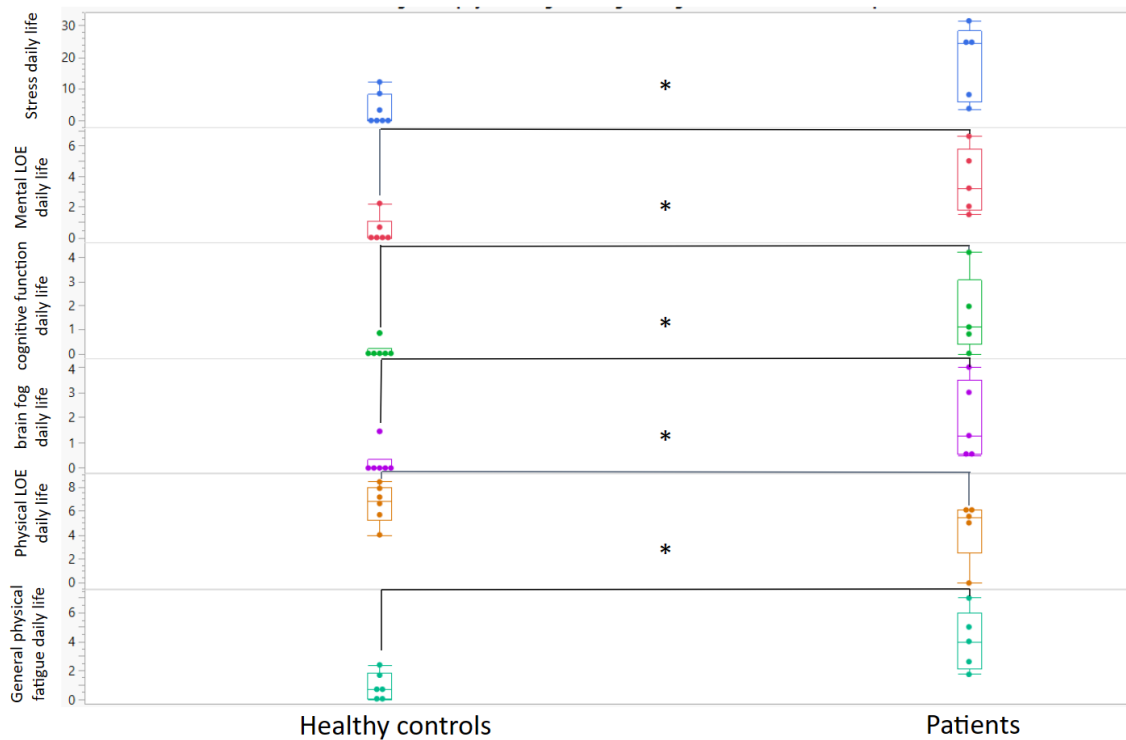


Figure 6. This figure shows the distribution and the difference between healthy controls (HC) and chronic fatigue syndrome patients for experience sampling methodology based variables after mental or physical activity for cognitive fatigue, physical fatigue and stress. *= $p < 0.05$ indicating significant results. "General physical fatigue daily life" ($p = 0.01$); "Mental loss of energy (LOE) daily life" ($p = 0.02$); "Brain fog daily life" ($p = 0.05$); "Cognitive function daily life" ($p = 0.02$) and "Stress daily life" ($p = 0.03$) were all significant compared to HC.

4.1.3 Difference scores during daily life

We found a significant result for the variable "Mental LOE daily life" ($p = 0.04$, median= 1.17 (-1.35-1.74) CFS and median= 0.89(0.39-2.17) HC). Indicating that CFS patients experience a higher Mental LOE from the rest condition to the activity condition compared to the healthy controls in their daily life. "Cognitive function daily life" ($p = 0.57$, median= 0.24(-0.29-0.70) CFS and median= 0(-0.01-0.05) HC); "General physical fatigue daily life" ($p = 0.46$, median= -0.5(-1.07-1.81) CFS and median= -0.04(-0.45-0.21)HC); "Physical LOE daily life" ($p = 0.78$, median= 1.17(-1.35-1.74) CFS and median= 0.89(0.39-2.17)HC); "Brain fog daily life"

($p=0.15$, median=0.66(-0.06-0.87) CFS and median= 0(-0.08-0) HC); “Stress daily life” ($p=0.51$, median=6.04(-2.16-13.20)CFS and median=0.14(0.06-6.40)HC) were not significant indicating that the CFS experience no difference compared to HC from rest condition to the activity condition. (Figure 7)



Figure 7. This figure shows the distribution and extent of difference between healthy controls and chronic fatigue syndrome patients for experience sampling methodology based variables: Mental loss of energy (LOE), cognitive function, physical LOE, general physical fatigue, Brain fog and stress. *= $p<0.05$ indicating significant results. “Mental LOE daily life” $p=0.04$ was significant from the rest condition to the activity condition.

4.1.4 CFS-related symptoms at baseline in the laboratory

We found a significant result for the variables “General physical fatigue before cycle test” ($p=0.004$, median= 5(3-6.5)CFS and median= 1(0-1) HC); “Physical LOE before cycle test” ($p= 0.003$, median= 4(2.5-6.5) CFS and median= 0(0-0) HC); “Cognitive function before the PASAT” ($p= 0.03$, median= 4(2-6) CFS and median= 2(0-3) HC); “Mental LOE before the PASAT” ($p= 0.03$, median= 4(2-6) CFS and median= 1(0-2) HC). Indicating that the patients experience significantly higher physical fatigue, more physical LOE, more loss of cognitive function and a higher mental LOE compared to the healthy controls during the laboratory

testing when they did not perform any physical or mental activity. “Stress before the MAST” ($p= 0.3$, median= 0.6(0-1.45) CFS and median= 0(0-0.52) HC); “Brain fog before the PASAT” ($p= 0.14$, median= 4(2-5.5) CFS and median= 2(0-3) HC) were not significant. (Figure 8)

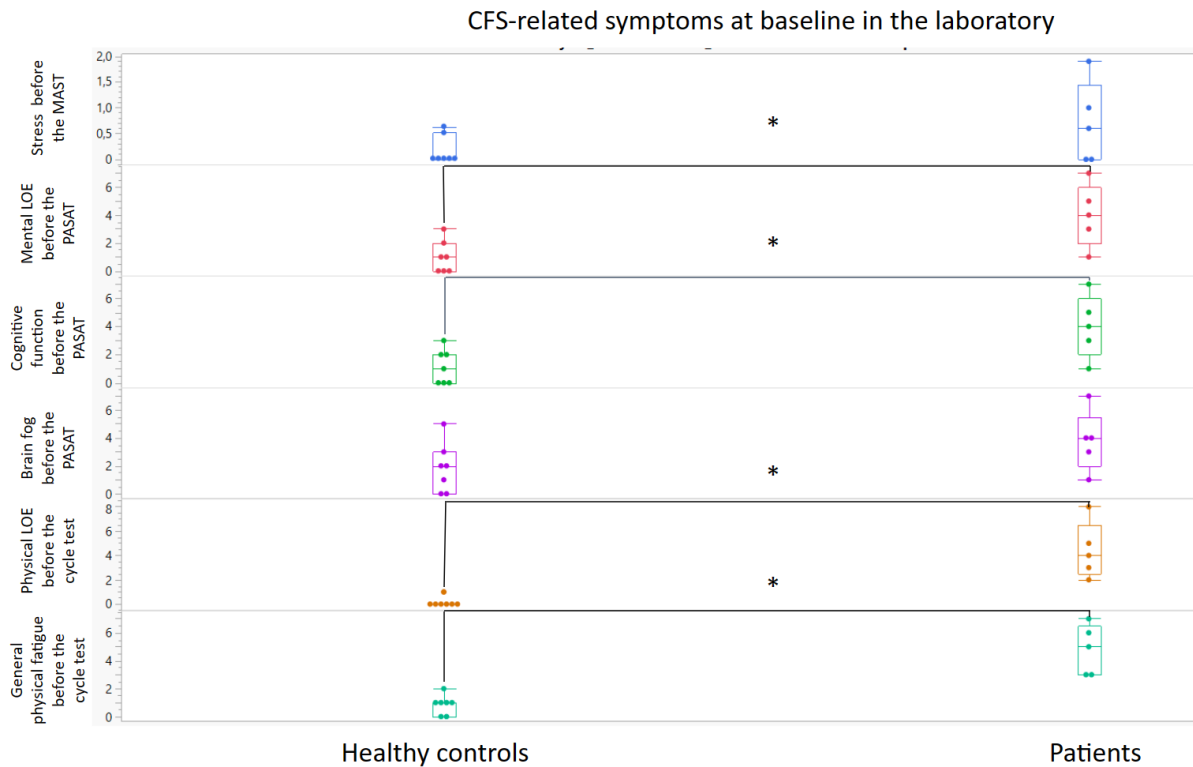


Figure 8. This figure shows the distribution and the difference between healthy controls and chronic fatigue syndrome patients for lab-based variables at baseline for general physical fatigue, physical loss of energy (LOE), Brain fog, cognitive function, Mental LOE and stress. *= $p < 0.05$ indicating significant results. “General physical fatigue before cycle test” ($p= 0.004$); “Physical LOE before cycle test” ($p= 0.003$); “Cognitive function before the paced auditory serial attention task (PASAT)” ($p= 0.03$) and “Mental loss of energy (LOE) before the PASAT” ($p= 0.03$) were significant.

4.1.5 CFS-related symptoms after exercise in the laboratory

We found a significant result for the variables “Physical LOE after cycle test” ($p= 0.01$, median= 7(6.5-8) CFS and median= 1(1-5) HC); “Cognitive function after PASAT” ($p= 0.01$, median= 5(3-6.5) CFS and median= 0(0-2) HC); and “Mental LOE after PASAT” ($p= 0.01$, median= 5(3-5) CFS and median= 1(0-1) HC). These results show that the patients

experience more physical LOE, more loss of cognitive function and a higher mental LOE compared to the patients healthy controls during the laboratory testing when they performed any physical or mental activity. “General physical fatigue after the cycle test” ($p=0.12$, median= 7(6-7.5) CFS and median= 4(0-7) HC); “Brain fog after the PASAT” ($p=0.08$, median= 5(3-5.5) CFS and median= 1(0-5) HC); “Stress after the MAST” ($p=0.42$, median= 6.55(1.28-9.58) CFS and median= 2.95(0.6-4.84) HC) were not significant. (Figure 9)

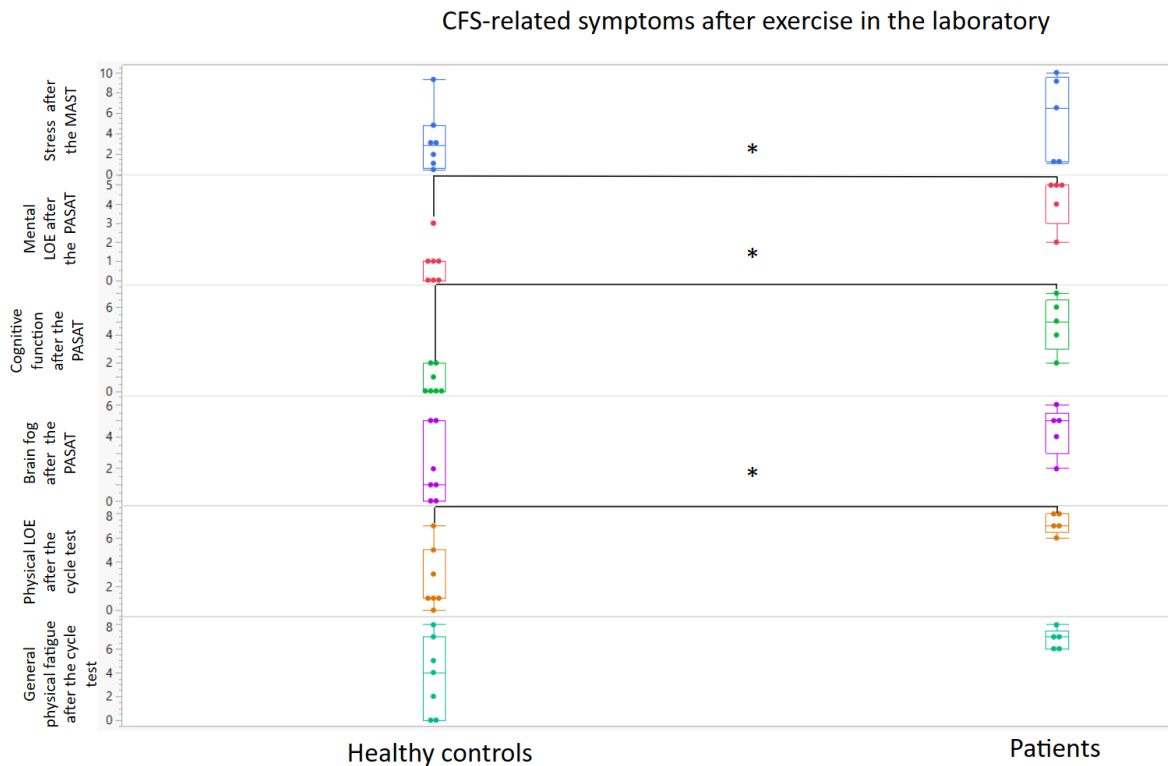


Figure 9. This figure shows the distribution and the difference between healthy controls and chronic fatigue syndrome patients for lab-based variables after physical or cognitive task for general physical fatigue, physical loss of energy (LOE), brain fog, cognitive function, mental LOE and stress. *= $p<0.05$ indicating significant results. “Physical LOE after cycle test” ($p=0.01$); “Cognitive function after paced auditory serial attention task (PASAT)” ($p=0.01$) and “Mental LOE after PASAT” ($p=0.01$) were significant.

4.1.6 Difference scores in the laboratory

We found no significant results for the laboratory difference score variables, meaning that, in contrast to the daily life measurements, the patients didn’t experience a higher increase in symptom experience from baseline to the exercise condition compared to the HC in the

laboratory. “General physical fatigue for the cycle test” (p= 0.87, median= 3(0.5-3) CFS and median= 3(0-6) HC); “Physical LOE for cycle test” (p= 0.81, median=3(1-4.5) CFS and median= 1(1-5) HC); “Brain fog for the PASAT” (p= 0.56, median= 0.66(-0.06-0.87) CFS and median= 0(-0.08-0) HC); “Cognitive function for the PASAT” (p= 0.32, median= 1(-1-2.5) CFS and median= -1(-2-2) HC); “Mental LOE for the PASAT” (p= 0.68, median= 0(-1-1.5) CFS and median= 0(-1-1) HC); “Stress for the MAST” (p= 0.52, median= 4.65(0.98-9.08) CFS and median= 2.95(0.6-4.84) HC) were all not significant. (Figure 10)

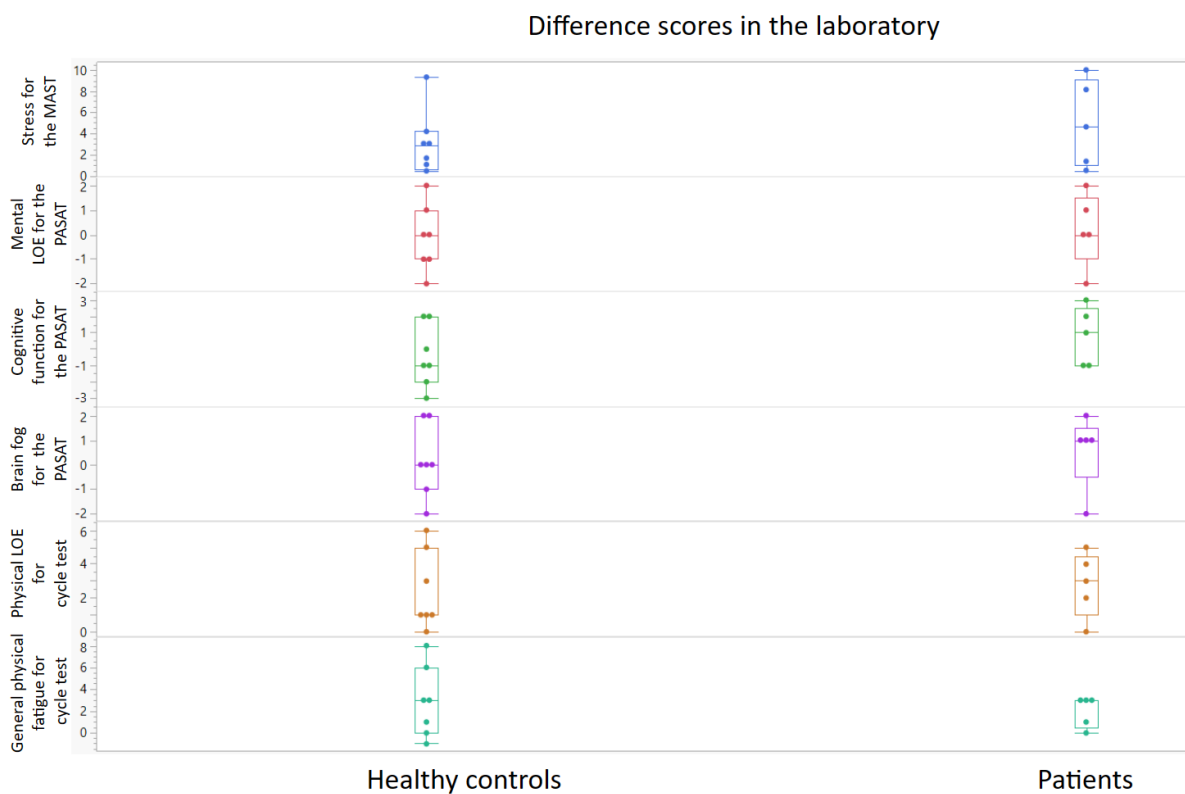


Figure 10. This figure shows the distribution and extent of difference between healthy controls and chronic fatigue syndrome patients for experience sampling methodology based variables: general physical fatigue, physical loss of energy (LOE), brain fog, cognitive function, mental LOE and stress. *= p<0.05 indicating significant results. There were no significant results for the laboratory difference score variables.

4.2 Comparing HR and HRV between CFS patients and HC

4.2.1 HR and HRV during rest

HR results prove that CFS patients have a significantly higher HR in rest compared to healthy persons “HR before the PASAT” ($p= 0.01$, median=84(78.61-95.84) CFS and median=65 (62.65-72.36) HC). Furthermore, the results show a trend for a lower HRV in patients compared to healthy controls “HRV Before PASAT” ($p=0.051$, median= 10.95(8.13-34.10) CFS and median=34.73(31.58-60.46) HC). (Figure 11)

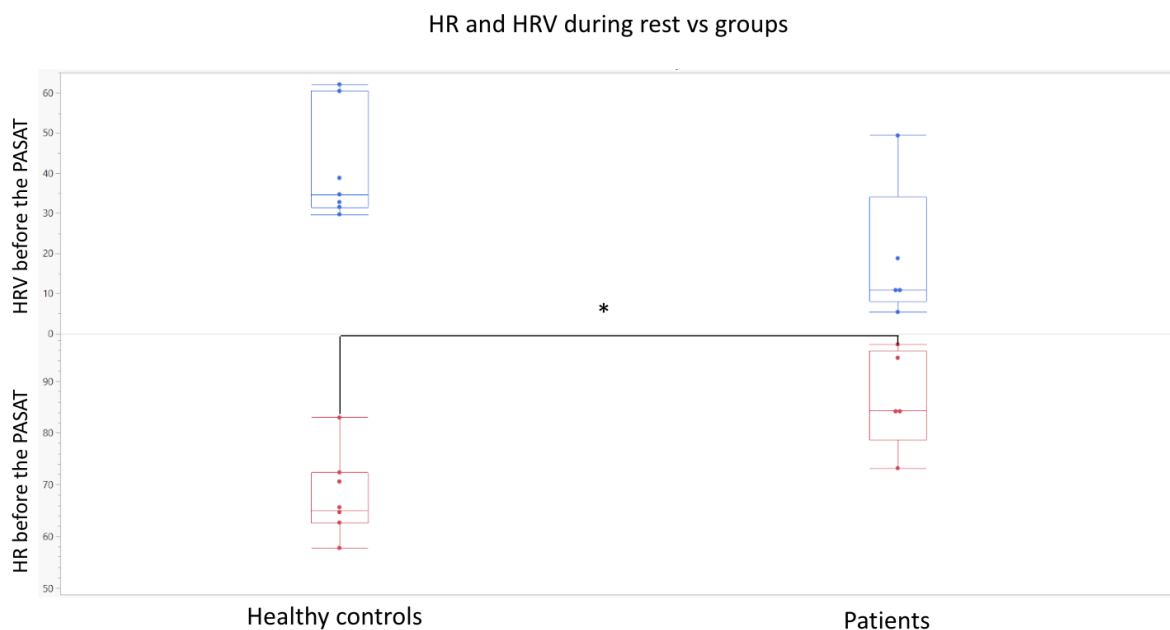


Figure 11. This figure shows the distribution and the difference between healthy controls and chronic fatigue syndrome patients for heart rate (HR) and heart rate variability (HRV) before the paced auditory serial attention task (PASAT). * = $p < 0.05$ indicating significant results. "HR before the PASAT" ($p: 0.01$) was significant and "HRV Before PASAT" ($p=0.051$) had a trend towards significance.

4.2.2 HR and HRV during a cognitive challenge

HR results prove that CFS patients have a significantly lower HRV during a mental activity compared to healthy controls “HRV after the PASAT” ($p= 0.01$, median=84.8(69.6-96.9) CFS and median=62.72(61.79-77.04) HC). Furthermore, the results show a trend for a higher HR

in patients compared to healthy controls “HR after the PASAT” ($p=0.051$, median=14.12(9.01-22.23) CFS and median=41.59 (27.99-59.59) HC). (Figure 12)

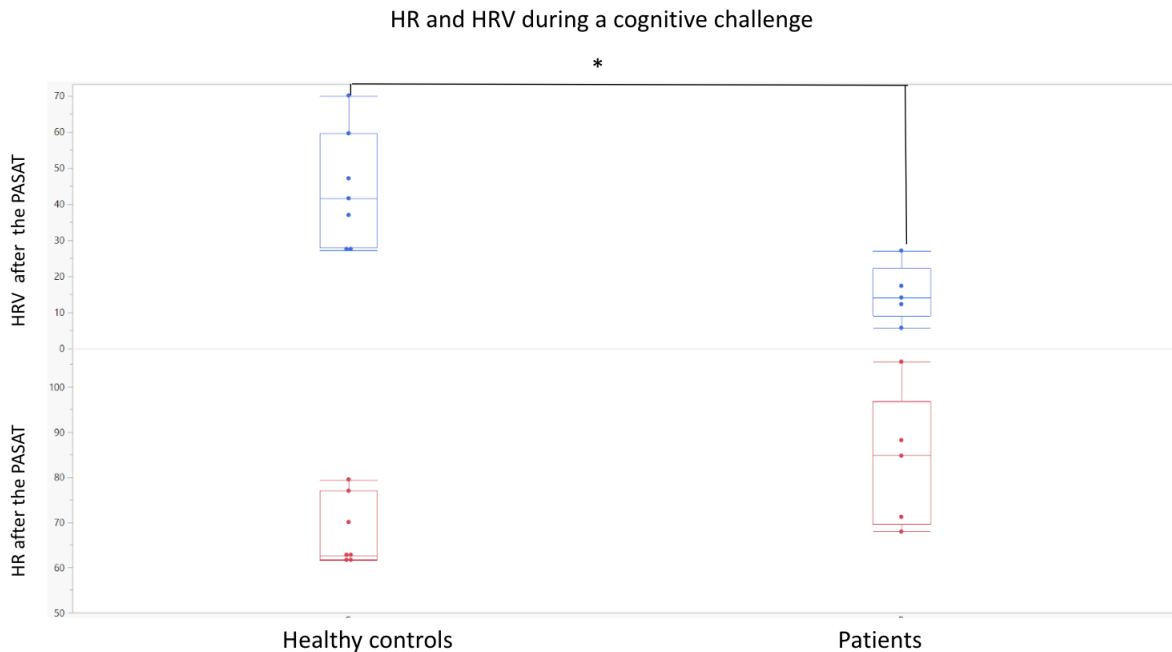


Figure 12. This figure shows the distribution and the difference between healthy controls and chronic fatigue syndrome (CFS) patients for heart rate (HR) and RMSSD after a cognitive challenge.*= $p<0.05$ indicating significant results. “Heart rate variability (HRV) after the paced auditory serial attention task (PASAT)”($p= 0.01$) is significant and “ HR after the PASAT” ($p= 0.051$) shows a trend for a higher HR in CFS compared to healthy controls.

4.3 Link between HRV and CFS-related symptoms

4.3.1 CFS-related symptoms and HRV in rest

HRV results prove that all participants have a significantly negative correlation between the variables “HRV before PASAT” and “Cognitive function before the PASAT” ($p= 0.04$, $\rho= -0.59$), “HRV before PASAT” and “Mental LOE before the PASAT” ($p= 0.02$, $\rho= -0.66$) and “HRV before PASAT” and “brain fog before the PASAT” ($p= 0.34$, $\rho= -0.30$). Indicating that a lower HRV is correlated with more loss of cognitive function and more mental LOE before the PASAT for all participants. (Figure 13)

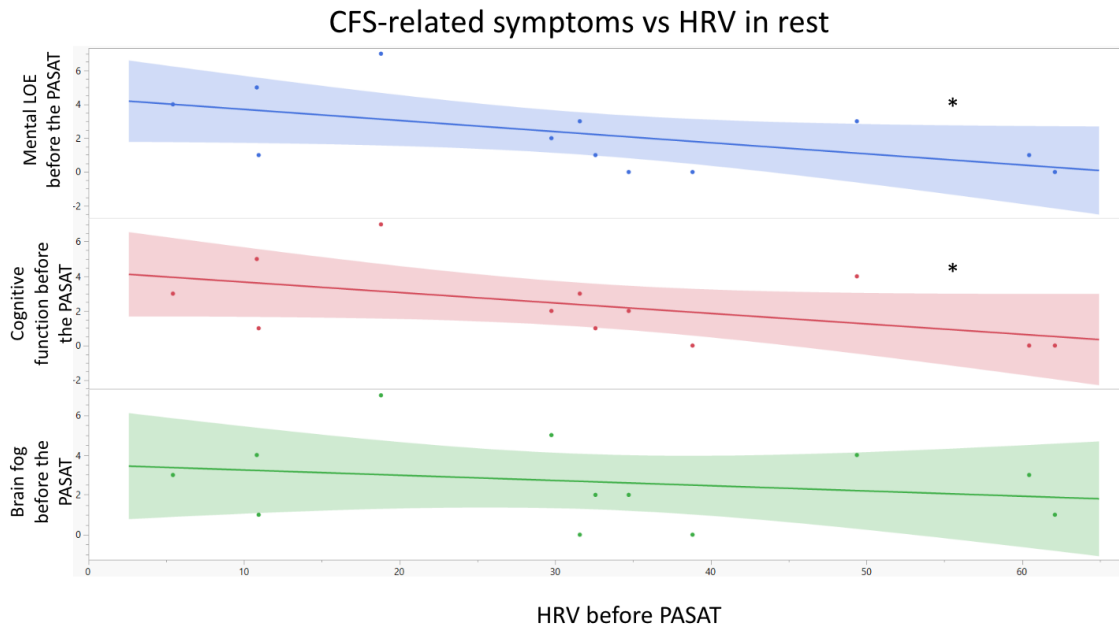


Figure 13. This figure shows the correlation at baseline between heart rate variability (HRV) and chronic fatigue syndrome symptoms before the paced auditory serial attention task (PASAT) for cognitive function, brain fog and Mental loss of energy (LOE). *= $p < 0.05$ indicating significant results. “HRV before PASAT” and “Cognitive function before the PASAT” ($p = 0.04$, $\rho = -0.59$), “HRV before PASAT” and “Mental LOE before the PASAT” ($p = 0.02$, $\rho = -0.66$) showed a significant negative correlation.

4.3.2 CFS-related symptoms and HRV during a cognitive challenge

HRV results prove that all participants have a significantly negative correlation between the variables “HRV after the PASAT” and “Brain fog after the PASAT” ($p = 0.05$, $\rho = -0.58$), between “HRV after the PASAT” and “cognitive function after the PASAT” ($p = 0.004$, $\rho = -0.76$), and between “HRV after the PASAT” and “Mental LOE after the PASAT” ($p = 0.002$, $\rho = -0.79$). Indicating that a lower HRV is correlated with more loss of cognitive function, more mental LOE before the PASAT and more brain fog after the PASAT for all participants. (Figure 14)

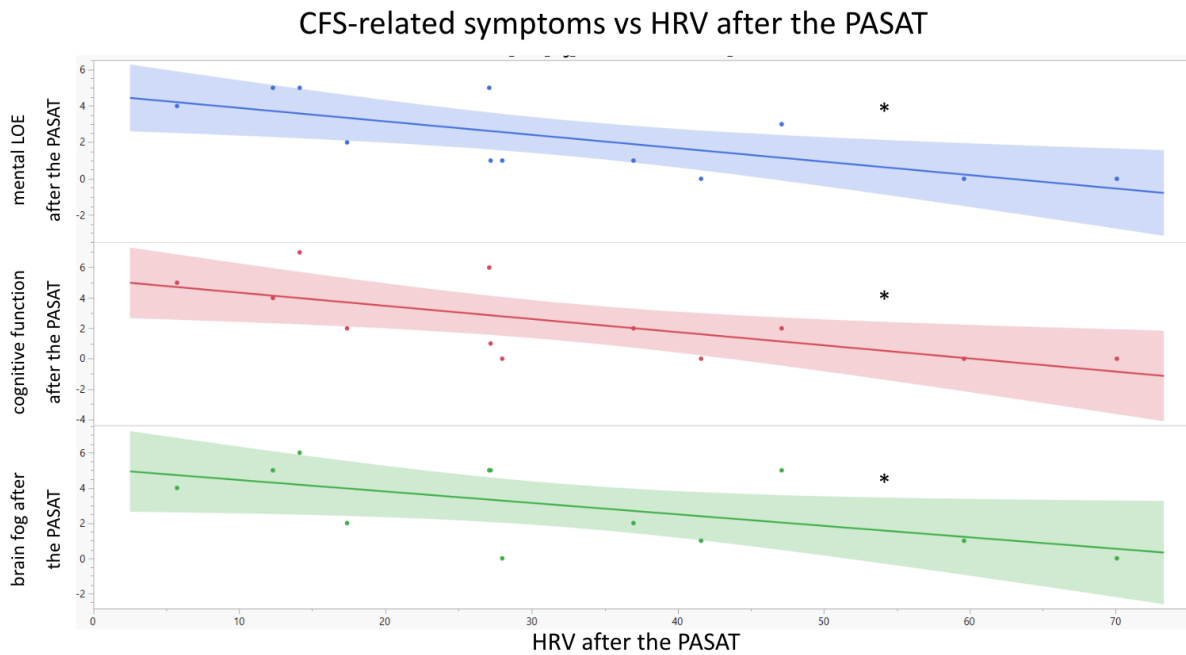


Figure 14. This figure shows the correlation after the paced auditory serial attention task (PASAT) between heart rate variability (HRV) and chronic fatigue syndrome patients symptoms after PASAT for cognitive function, brain fog and Mental loss of energy (LOE). *= $p < 0.05$ indicating significant results. “HRV after the PASAT” and “brain fog after the PASAT” ($p: 0.05$, $\rho: -0.58$), “HRV after the PASAT” and “cognitive function after the PASAT” ($p: 0.004$, $\rho: -0.76$) and “HRV after the PASAT” and “mental LOE after the PASAT” ($p: 0.002$, $\rho: -0.79$) showed a significant negative correlation.

4.3.3 Comparing HRV at rest and during a cognitive challenge

There was no significant difference between “HRV before PASAT” ($p > t = 0.98$, median=32.09(12.91-46.75) and “HRV after PASAT” median= 27.59(14.93-45.73) for all participants). Indicating that there is no significant difference in HRV between baseline and during the PASAT’.

Comparing HRV at rest and during a cognitive challenge vs all participants

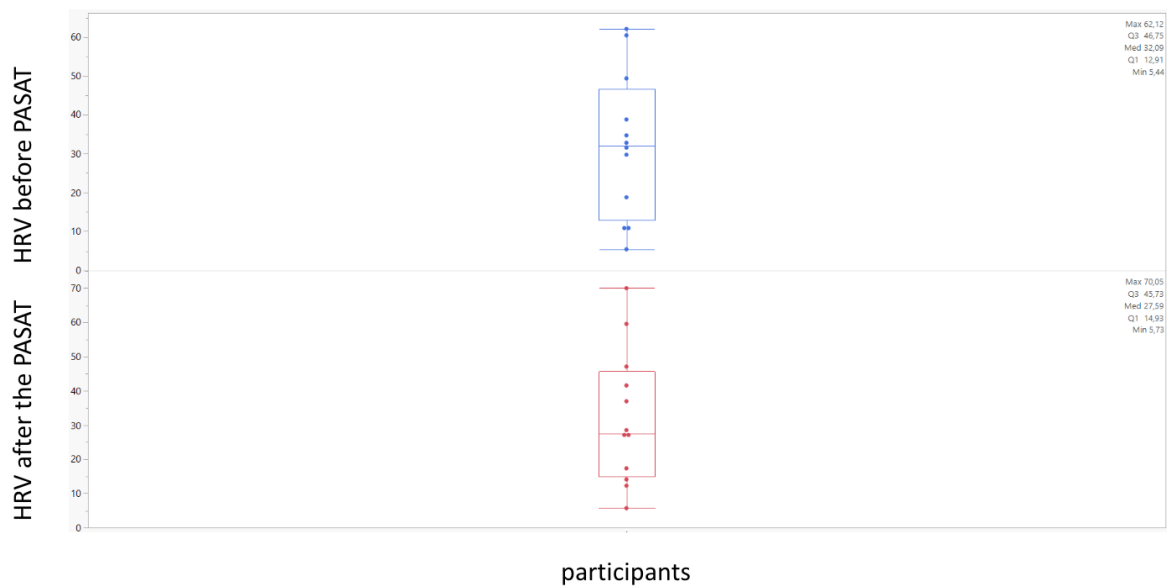


Figure 15. This figure shows the distribution of “heart rate variability (HRV) before the paced auditory serial attention task (PASAT)” and “HRV after the PASAT” for all participants. $*=p<0.05$ indicating significant results. There was no significant difference between “HRV before the PASAT” and “HRV after the PASAT” ($p>t= 0.98$) for all participants.

5. Discussion

Our study included five patients, who got a diagnosis of CFS according to the 1994 Centers for Disease Control and Prevention Fukuda criteria, and seven healthy controls. The study's first aim was to compare symptom experience in CFS patients and healthy controls during laboratory measurements and in their daily life. Next, we investigated the link between symptom experience in the laboratory and in daily life in both patients and healthy subjects. Furthermore, we aimed to compare the HR and HRV between patients and healthy participants and we wanted to determine the difference between HRV in rest and during a cognitive challenge. Finally, we aimed to identify a link between CFS-related symptoms and HRV measurements.

5.1 Symptom experience in CFS patients vs. healthy controls: lab vs. daily life

After comparing symptom experience at rest between patients and healthy subjects, our results showed that patients experienced more physical fatigue and cognitive fatigue in daily life. In a laboratory environment, patients also reported more loss of physical energy and more cognitive problems in addition to increased levels of physical and cognitive fatigue. These results are in accordance with our expectations and with results of (Ocon, 2013; Solomon et al., 2003; Miller et al., 2014). We did not find a significant difference in the experience of stress and brain fog between patients and healthy participants. These outcomes are not in line with our expectations as well as with the results of (Balinas et al., 2021; Ocon, 2013), showing a significant altered experience for these variables in patients. However, it is possible that these non-significant results are caused by the small, and probably heterogeneous, sample that was included in our study.

According to what we expected and to the results of several studies (Keech et al., 2015; Cook et al., 2017; Cvejic et al., 2017; Light et al., 2009), our findings in the exercise conditions proved that patients also experienced significantly more physical fatigue, cognitive fatigue, cognitive problems, brain fog and stress in their daily life compared to healthy persons and significantly more loss of physical energy levels, more cognitive fatigue and more cognitive problems in a laboratory setting.

In contrast, we failed to find a significantly greater increase in physical fatigue and loss of physical energy levels from baseline to exercise in patients compared to healthy subjects in both daily life and a laboratory setting. These results were contrary to our expectations. Previous studies often reported about the role of post-exertional malaise (PEM) as a characteristic symptom of CFS patients in comparison with healthy persons (Keech et al., 2015; Cook et al., 2017; Cvejic et al., 2017). It is possible however that the time period that we took into account to study post-exercise symptomatology, was too limited. We performed symptomatology measurements immediately after the cycling task. The study of Yoshiuchi et al. (2007) for example, demonstrated an increase in physical fatigue five days after performing a similar physical task as the one used in our study.

Our results show that, in a daily life setting, patients have a higher increase in mental fatigue from the baseline condition to exercise condition compared to healthy subjects. These findings are in accordance with the ones reported in for example the study of Mizuno et al. (2011). They demonstrated an increase in cognitive exhaustion in response to mental activity during their daily life. However, our laboratory findings did not reveal any significant difference between patients and healthy controls concerning the changes in cognitive fatigue scores throughout the PASAT. This is in contrast to what we expected and also to findings of Cook et al. (2007), who also performed the PASAT, and Keech et al. (2015). These studies showed a greater increase in fatigue levels throughout the mental tasks in patients than in healthy persons. However, just like for physical fatigue, it is possible that patients will experience more feelings of cognitive fatigue for a longer duration than healthy controls. Therefore, it would be useful to also perform cognitive fatigue measurements a few hours after the PASAT.

As well in daily life as in the laboratory, the changes in cognitive problems and brain fog levels throughout cognitive activity situations, do not differ significantly between patients and healthy controls. These results are in line with the study of Yoshiuchi et al. (2007), who also demonstrated no difference between patients and healthy controls concerning cognitive functioning after executing a cognitive task.

Finally, the results show no significant differences in the changes in stress experience from baseline throughout stressful situations in daily life and in the lab. This is not what we expected as numerous studies report about the dysfunctional stress responses in CFS patients. However, the study sample investigated in this study is rather small and possibly also heterogeneous. Therefore, it is possible that a dysfunctional stress-response system is not a core characteristic of (the majority of) our patient sample. In addition, in our study we only took subjective stress into account. The MAST has previously shown to induce HPA axis reactivity with increase in cortisol levels. Therefore, also taking objective parameters, like cortisol, into account, would result in more reliable and complete outcomes.

We did not find a significant correlation between the difference scores of CFS-related symptoms reported in the laboratory and daily life, suggesting that the change in symptoms in response to a physical, cognitive or stressful situation in daily life is not an adequate reflection of the experiences during laboratory tasks. Several factors can attribute to this fact. First, laboratory-based assessments are performed in a controlled environment and the instructions don't reflect the complexity and diversity of daily life events. Further, the sense of being watched by the researcher in the laboratory can alter the symptomatology experienced by the participant (Berthelot et al., 2019). Third, it is possible that assessments may not fully capture the symptoms experienced by our limited sample. CFS is a heterogeneous condition, in which the symptoms and the triggers for the symptoms can differ between patients.

5.2 Comparing heart rate and heart rate variability in CFS patients and healthy controls: rest vs. cognitive challenge and the link with the symptoms

Our baseline results showed a higher HR and a trend towards lower HRV in patients compared to healthy subjects. These results are in accordance with the results of Meeus et al. (2013) who found a reduced HRV in CFS during sleep, Boneva et al. (2007) reporting an increased HR and reduced HRV in CFS during sleep, Rimes et al. (2017) who found a significant lower HRV at baseline and Egge & Wyller (2010) who found a higher HR in rest in CFS.

During a cognitive challenge, the analyses demonstrated a trend towards significance for a higher HR and a significantly lower HRV in patients compared to healthy controls. This is consistent with the study of Beaumont et al (2012) showing that CFS patients have a low HRV and greater HR reactivity after a cognitive challenge. A lower HRV means that the heart rate can less easily adapt to changing stressors. Therefore, lower HRV in patients suggests the role of sympathetic hyperactivation and decreased parasympathetic activity in the pathophysiology of the disorder. As a result, we can agree with other studies suggesting that dysfunctions of ANS can play a role in the pathology of CFS patients.

Escorihuela et al. (2020) demonstrated that lower HRV in rest is associated with fatigue severity in CFS patients. Consistent with their results, we showed an inverse association between HRV in rest and cognitive fatigue as well as between HRV in rest and cognitive problems. Furthermore, in accordance with our results of the correlations in the rest condition, we show an inverse relationship between HRV measurements during a cognitive challenge and cognitive fatigue, cognitive problems and brain fog. This is consistent with the study of Beaumont et al (2012), who found a correlation between a lower HRV and poorer function of neurocognitive tasks. These results show that lower HRV is associated with a higher symptom experience in rest as well as during a cognitive challenge. Accordingly, we did not find any significant differences between HRV in rest and HRV during a cognitive challenge.

5.3 Strengths and limitations

One strength of this study is that CFS patients are included through evaluation by internists and psychiatrists with expertise in fatigue assessments according to the 1994 Centre of Disease Control and Prevention Fukuda criteria. Furthermore, for the laboratory measurements in the study, we used validated tasks like the MAST which is a test to induce objective and subjective stress responses, the PASAT and the arm-leg cycle test, which are both validated tasks to induce cognitive and physical fatigue, respectively. In addition, we used the FES to assess feelings of both physical and cognitive fatigue, which is a validated scale to determine feelings of fatigue in CFS patients. Next, in addition to the laboratory measurements mostly used in studies, this study also used the ESM to investigate the

symptoms in daily life. Finally, the order of the lab tests was carefully chosen to minimize the effect of weariness from one test to the next.

However, the study also had a few limitations. First, we used a small sample size. We included five CFS patients and seven healthy controls. Therefore, it is difficult to generalize the findings to all patients with CFS. As we reported earlier, the CFS patient population is probably very heterogeneous. Secondly, not every patient experiences the same symptoms and not every patient has the same (psycho)physiological dysfunctions. It is important to take these interindividual differences into account in future studies. Thirdly, another disadvantage of the study is that, due to the small sample size, we were unable to perform the correlation analyses on the two groups separately. Therefore we did the correlation analyses by taking the results of both groups together. Fourthly, our study encountered some missing data of two subjects (one healthy control and one participant) for the daily life measurements of brain fog, cognitive function at rest and during an activity, mental LOE, and the difference scores of these variables. In addition, there was missing data of one healthy control concerning the daily life measurements of general physical fatigue, physical LOE and their difference scores. Fifthly, during the study procedure, we increased the length of the arm-leg cycle test from fifteen to 25 minutes. As a result five participants (of which two CFS patients) performed a fifteen minute cycling test and seven participants (of which three CFS patients) performed a cycling test of 25 minutes. Both results were used in the analysis of our study.

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Appendix A:

Home-based assessment (ESM): Questions used for this thesis are marked in yellow

1. Vragen in verband met vermoeidheid: antwoordmogelijkheid met een slider van 0 = 'geen' tot 10= 'absolute maximum'

- Op dit moment voel ik me fysiek uitgeput (fysiek uitgeput)
- Op dit moment voel ik me fysiek vermoeid (fysieke vermoeid)
- Op dit moment ervaar ik een gevoel van zware benen (zware benen)
- Mijn fysieke energie is (lichamelijke vitaliteit)

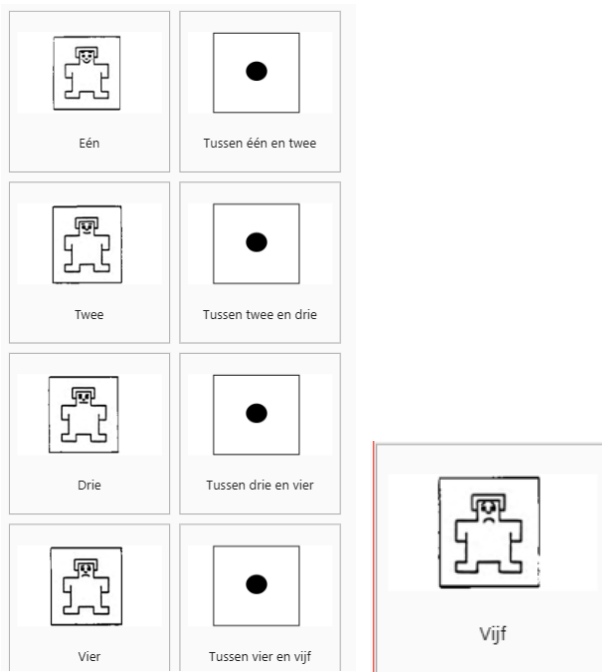
- Op dit moment ervaar ik mist in mijn hoofd (hersennmist)
- Op dit moment ervaar ik concentratieproblemen (moeilijkheden concentratie)
- Op dit moment voel ik me gedesoriënteerd (gedesoriënteerd)
- Op dit moment voel ik me mentaal vermoeid (mentaal vermoeid)
- Op dit moment ervaar ik geheugenproblemen (moeilijkheden met geheugen)
- Op dit moment voel ik me mentaal uitgeput (mentale uitputting)

2. Vragen omtrent de gevolgen van vermoeidheid: antwoordmogelijkheid met slider van 0= 'helemaal niet' tot 100= 'absolute maximum'

- Sinds de vorige biëp piekerde ik over mijn vermoeidheid (symptoom focus)
- Sinds de vorige biëp richtte ik mijn aandacht op vermoeidheid (selective attention)
- Sinds de vorige biëp vermeid ik een bepaalde activiteit om gevoelens van uitputting te vermijden (vermijding)

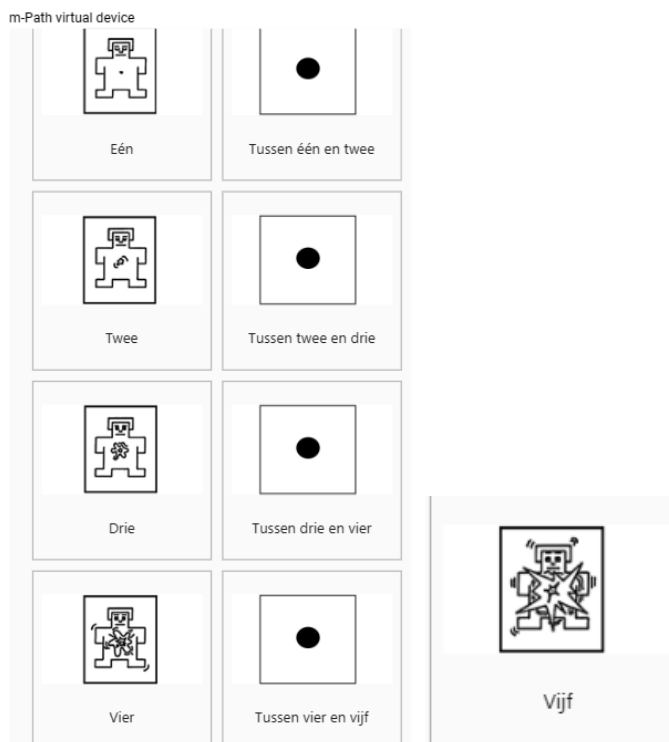
3. Vraag in verband met Valentie: antwoordmogelijkheid via afbeelding mogelijkheden (zie hieronder)

- Duid het eerste mannetje aan indien u zich compleet blij voelt. Duid het laatste mannetje aan indien u zich compleet niet blij voelt. Duid een andere optie aan indien uw gevoelens zich tussen de twee uitersten bevinden. Druk daarna op 'volgende vraag' (valentie tekst)



4. Vraag in verband met de arousal: antwoord mogelijkheid via afbeelding mogelijkheden (zie hieronder)

- Duid het eerste mannetje aan indien u zich compleet kalm voelt. Duid het laatste mannetje aan indien u zich helemaal opgewonden voelt. Duid een andere optie aan indien uw gevoelens zich tussen de twee uitersten bevinden. Druk daarna op 'volgende vraag' (arousal tekst)



5. Vraag in verband met stress/ nervositeit: antwoordmogelijkheid met slider van 0= 'helemaal niet' tot 100= 'absolute maximum'

- Op dit moment voel ik me gestresseerd (stress)
- Op dit moment voel ik me nerveus (nerveus)
- Ik voel me comfortabel in de omgeving waar ik nu ben (omgeving)

6. Vraag in verband met activiteit:

- Vijf minuten of minder voor de biep afging voerde ik een fysieke activiteit uit (fysieke activiteit): met de volgende antwoordmogelijkheden:
 - o Geen fysieke
 - o Lichte fysieke activiteit
 - o Gematigde fysieke activiteit
 - o Zware fysieke activiteit
- Vijf minuten of minder voor de biep afging, leverde ik een mentale inspanning: antwoordmogelijkheid met slider van 0='helemaal' niet tot 100= 'absolute maximum'

7. Vraag in verband met activiteit:

- Denk aan wat je aan het doen was vijf minuten of minder voor de biep afging. Met de onderstaande follow u vragen met antwoordmogelijkheden via slider van 0='helemaal niet' tot 100= 'absolute maximum'
 - o Deze activiteit vergde moeite (moeite fysieke activiteit)
 - o Ik deed liever iets anders (belangrijk fysieke activiteit)
 - o Ik genoot van deze activiteit (genot fysieke activiteit)

8. Vraag in verband met de rust:

- Heb je sinds de vorige biep gerust (rust): met multiplechoice antwoordmogelijkheden tussen ja en nee

9. Vragen in verband met de symptomen: antwoordmogelijkheid met slider van 0= 'helemaal niet' tot 100= 'absolute maximum'

- Op dit moment heb ik last van kortademigheid (kortademigheid)
- Op dit moment heb ik een snellere hartslag (hartslag)
- Op dit moment heb ik hoofdpijn (hoofdpijn)
- Op dit moment heb ik gewrichts-of spierpijn (gewrichts-of spierpijn)

10. Vraag in verband met substantie gebruik: met onderstaande multiplechoice antwoordmogelijkheden

- Cafeïne
- Nicotine
- Alcohol
- Medicatie
- Drugs
- Eten
- Geen van bovenstaande

Appendix B:

the Fatigue and Energy Scale (FES):

Vermoeidheids- en energieschaal

Geef aan in welke mate u elk symptoom op dit moment ervaart (omcirkel uw gekozen nummer voor elk item hieronder). Lees de beschrijvingen bij elk item eerst aandachtig.

	Op dit moment voel ik me/ ervaar ik een gevoel van..	Beschrijving	Geen	Juist merkbaar	Minimaal	Mild	Mild-gematigd	Gematigd	Gematigd-hoog	Hoog	Zeer hoog	Extrem hoog	Absolute maximum
Fysiek	Algemene vermoeidheid	"uitputting"/"vermoeid"	0	1	2	3	4	5	6	7	8	9	10
	Fysiek functioneren	"zwaar gevoel in de ledematen"	0	1	2	3	4	5	6	7	8	9	10
	Daling in energiepeil	"fysiek leeg"/"lage vitaliteit"	0	1	2	3	4	5	6	7	8	9	10
Mentaal	Algemene vermoeidheid	"mist in het hoofd"/"wazig"	0	1	2	3	4	5	6	7	8	9	10
	Cognitief functioneren	"moeilijkheden met geheugen of concentratie"/"gespannen"/"gedesoriënteerd"	0	1	2	3	4	5	6	7	8	9	10
	Daling in energiepeil	"mentaal leeg"	0	1	2	3	4	5	6	7	8	9	10