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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesietherapie

Masterthesis

Autonomic stress reactivity in patients with medically unexplained physical symptoms

Aline De Wit
Amber Gielen

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesietherapie, afstudeerrichting revalidatiewetenschappen en kinesietherapie bij kinderen

PROMOTOR :

Prof. dr. Katleen BOGAERTS

BEGELEIDER :

Mevrouw Indra RAMAKERS

COPROMOTOR :

dr. Maaïke VAN DEN HOUTE



UHASSELT

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www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

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Kruisstraat 27, 3980 Tessenderlo, 7/06/2021

A.D.W.

Houbenstraat 15, 3670 Oudsbergen, 7/06/2021

A.G.

RESEARCH CONTEXT

The master's thesis is part of the master's program in Rehabilitation Sciences and Physiotherapy. This study is part of the research domain of mental health care. The aim of this study is to investigate the autonomic stress reactivity in patients with medically unexplained physical symptoms (overstrain, burnout and functional somatic syndromes), compared to patients with panic disorder and compared to healthy individuals. Some research has been conducted looking at the autonomic nervous system in the different patient groups. However, no research has been done comparing the different groups with each other, so it is important that this is investigated further.

The study was conducted by two students Rehabilitation Sciences and Physiotherapy at Hasselt University. This was done with the support of Prof. Dr. K. Bogaerts, Dr. M. Van Den Houte and Dra. I. Ramakers. The research is part of a larger project: "Physiological stress reactivity in patients with stress-related complaints". This was in collaboration with the Multidisciplinary Expertise Center Tumi Therapeutics (Heusden-Zolder, Belgium) and the Faculty of Psychology and Educational Sciences, KULeuven (Leuven, Belgium).

The study is written according to the central format. The research questions were determined in consultation with Dr. M. Van Den Houte and Dra. I. Ramakers. The students did not have any part in determining the research design and method as the study was part of an ongoing research project. The recruitment of the patients and data acquisition had already been performed, the students did not have any contribution to this. The visual inspection of the data was done by the students themselves. Dr. M. Van Den Houte and Dra. I. Ramakers performed the statistical analysis. The interpretation of the results was performed by the students.

The academic writing process was also performed by the students. Dr. M. Van Den Houte and Dra. I. Ramakers provided the students with feedback to further improve the paper.

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AUTONOMIC STRESS REACTIVITY IN PATIENTS WITH MEDICALLY UNEXPLAINED PHYSICAL SYMPTOMS

“Comparison with panic disorder patients and healthy controls”

Aline De Wit & Amber Gielen

Promotor: Prof. Dr. K. Bogaerts

Co-promotor: Dr. M. Van Den Houte

Mentor: Dra. I. Ramakers

1. Abstract

Background: Medically unexplained physical symptoms are common in primary care and can occur in the form of stress-related complaints or as functional somatic syndromes. A dysregulation of the autonomic stress physiology is often suggested as an underlying mechanism.

Objectives: Investigate the autonomic stress reactivity in patients with medically unexplained physical symptoms, compared to patients with panic disorder and compared to healthy controls.

Participants: The study included 105 patients (26 fibromyalgia/chronic fatigue syndrome, 35 burnout, 24 overstrain and 20 panic disorder) and 30 healthy controls. Patients were recruited through the Multidisciplinary Expertise Center Tumi Therapeutics (Heusden-Zolder, Belgium), while healthy controls were recruited through flyers and social media.

Measurements: All subjects completed a standardized stress test, consisting of a baseline measurement followed by three stressors (the Stroop color word task, the Mental Arithmetic Task and a stress talk). Each stressor was followed by a recovery phase. Heart rate was measured continuously during rest, the various stressors and recovery.

Results: The patients with fibromyalgia/chronic fatigue syndrome and panic disorder patients showed a higher heart rate compared to healthy controls during the baseline and recovery periods. The healthy controls had a steeper decline in heart rate compared to the overall patient group during the Stroop color word task and the stress talk.

Conclusion: A predominance of the sympathetic nervous system was found in patients with fibromyalgia/chronic fatigue syndrome, as well as in patients with panic disorder. No difference in autonomic stress reactivity was found between overstrain, burnout and fibromyalgia/chronic fatigue syndrome, suggesting that central processes (e.g. interoception and symptom perception), play a role in the development of functional somatic syndromes.

Keywords: Medically unexplained physical symptoms, overstrain, burnout, functional somatic syndromes, fibromyalgia, chronic fatigue syndrome, autonomic stress reactivity, stressor, heart rate

2. Introduction

Medically unexplained physical symptoms (MUPS) have a prevalence of 40% to 49% in primary care (Haller, Cramer, Lauche, & Dobos, 2015). Some common complaints are fatigue, dizziness, palpitations, headaches and nausea. These complaints cannot be (sufficiently) explained by a structural medical dysfunction (Olde Hartman et al., 2013). MUPS can occur in the form of stress-related complaints, such as overstrain and burnout, or as functional somatic syndromes (FSS), for example fibromyalgia (FM) and chronic fatigue syndrome (CFS). A dysregulation of stress physiology has been suggested as an underlying mechanism of these symptoms and syndromes.

The literature confirms that there is a stress continuum with stress complaints, overstrain and burnout from left to right (Bastiaanssen, Loo, Terluin, et al., 2011; Terluin, Van der Klink, & Schaufelis, 2005; Van Der Klink & Van Dijk, 2003; Verschuren, 2010). This continuum is based on the chronicity and severity of the symptoms. FSS is expected to be located far on the right of the stress continuum, but this has yet to be investigated (Tak & Rosmalen, 2010). In addition, McTeague and Lang (2012) described an anxiety continuum, in which anxiety disorders on the left of the continuum are characterized by an exaggerated startle reflex, while disorders on the right are characterized by a blunted response. This was explained by a depletion of the stress response, so this creates a similarity between both continuums.

Overstrain includes symptoms such as irritability, anxiety or feelings of depersonalization or derealization, with a rushed feeling and being unable to relax as main symptoms. Burnout contains the same symptoms, with a feeling of exhaustion as the main symptom, but is only diagnosed if the symptoms have been present for more than six months (Bastiaanssen, Loo, Terluin, et al., 2011; Van Der Klink & Van Dijk, 2003; Verschuren, 2010). A dysregulation of the autonomic nervous system (ANS) is suggested as an underlying mechanism in burnout (Danhof-Pont, van Veen, & Zitman, 2011; Schwartz et al., 2003). Several studies have already shown dysfunction of the ANS in FM and CFS (Martínez-Martínez, Mora, Vargas, Fuentes-Iniestra, & Martínez-Lavín, 2014; Van Cauwenbergh et al., 2014). This could be the common underlying pathogenesis, possibly explaining the overlap between the clinical features in FM and CFS (Martínez-Martínez et al., 2014).

Panic disorder (PD) includes the same physical symptoms as overstrain and burnout, but this is located on the anxiety continuum (Hassink-Franke et al., 2012). In PD, the ANS is also

believed to be dysregulated (Cohen et al., 2000). Due to the similarities between the physical complaints in patients with PD and patients with MUPS, it is interesting to investigate possible common mechanisms between the disorders and these two continuums.

The function of the ANS has often been investigated by means of a heart rate analysis, because during acute stress the sympathetic nervous system is activated and this causes an increase in the heart rate (HR) (Danhof-Pont et al., 2011). The sympathetic and parasympathetic nervous systems have been proven to play an important role in the regulation of the stress response (Ulrich-Lai & Herman, 2009).

An increased HR at baseline and during a stressor has been reported in burnout patients compared to healthy controls (HC) (Danhof-Pont et al., 2011; De Vente, Olf, Van Amsterdam, Kamphuis, & Emmelkamp, 2003). Van Cauwenbergh et al. (2014) reported a smaller increase in HR in CFS patients compared to HC during a mental stressor. In FM patients a higher HR was found during a stressor compared to HC (Collet, Averty, & Dittmar, 2009; Thieme et al., 2006), but they also showed a blunted response (González et al., 2019; Nilsen et al., 2007). However, these studies report conflicting results, and it is therefore important that this is investigated further. Only a comparison was made between patients and HC, but it is also interesting to compare the patient groups with each other. Little research has been done on overstrain and its relationship with the ANS, so this needs to be examined further as well. In PD, an increased HR was also found at baseline and during a stressor (Cohen et al., 2000; Limmer, Kornhuber, & Martin, 2015), and this group must also be compared with the patient groups.

The aim of this study is to investigate the autonomic stress reactivity (ASR) in patients with MUPS (overstrain, burnout and FSS), compared to patients with PD and compared to HC. HR will be continuously measured at rest, during various stressors and during recovery. Following research questions are considered: is there a dysregulation of the ASR between the patient groups and the HC, and what is the difference between these groups? Is there a difference in ASR between patients with MUPS and PD?

We expect a steeper incline of HR and higher HR values during the stressors, and a slower recovery after the stressors in patients compared to HC. ASR is expected to be more disturbed in disorders left on the stress continuum than right on this continuum. We also explore the difference in HR between patients with MUPS and PD.

3. Methods

3.1. Participants

Patients were recruited through the Multidisciplinary Expertise Center Tumi Therapeutics (Heusden-Zolder). The patient group consisted of patients with MUPS (overstrain, burnout and FSS, more specifically CFS and/or FM) and patients with PD. Patients with overstrain and burnout were diagnosed according to the multidisciplinary guidelines for overstrain and burnout for first line professionals of the NVAB (Nederlandse Vereniging van Arbeids- en Bedrijfsgeneeskunde) (Bastiaanssen, Loo, & Terluin, 2011). Patients with CFS had to meet the CDC criteria for CFS (Fukuda et al., 1994), and were diagnosed by a multidisciplinary team in the CFS-reference center UZ Leuven, while FM patients had to meet the ACR criteria (Cascade, 2000), and were diagnosed by a rheumatologist. PD was diagnosed according to the DSM-IV criteria with the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Overbeek, Schruers, & Griez, 1999; Sheehan et al., 1998).

HC were recruited through flyers and social media. The HC group consisted of individuals without a psychiatric or chronic medical condition. Participants were included in the HC group if they were between 18 and 65 years old. They also had to experience few physical complaints and little negative affect in daily life, for which a modified version of the Checklist for symptoms in Daily Life (CSD) (Wientjes & Grossman, 1994) and the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) were used for screening. HC were only included if they scored ≤ 70 on the CSD and ≤ 21 on the PANAS (Bogaerts, Janssens, De Peuter, Van Diest, & Van den Bergh, 2010; Bogaerts et al., 2008; Bogaerts et al., 2015; Bogaerts, Van Eylen, et al., 2010). Exclusion criteria for the HC group were pregnancy, Body Mass Index (BMI) <18 or >35 , presence or history of a psychiatric condition (screened by the M.I.N.I.), self-reported presence or history of a (chronic) medical illness, and taking psychotropic medication. It was ensured that the distribution between men and women and the distribution of the different age categories was the same within the patient group and within the control group (= frequency matching).

On the day of testing, the informed consent was given to the subjects, and this had to be signed before they could participate in the study. Before the start of the study, all participants

were informed about the purpose of the study, the procedure and the measurements. This study was initially approved by the Social and Societal Ethics Committee KULeuven (S58920) on 21/03/2016. The amendment was approved by the EC Research UZ/KULeuven on 31/07/2018.

3.2. Design

This study was part of a larger project: “Physiological stress reactivity in patients with stress-related complaints”. This investigation was in collaboration with the Multidisciplinary Expertise Center Tumi Therapeutics (Heusden-Zolder, Belgium) and the Faculty of Psychology and Educational Sciences, KULeuven (Leuven, Belgium).

All subjects underwent the same stress physiological examination. In the patient groups this was done by therapists from Tumi Therapeutics as part of the diagnostic intake procedure, and the researchers of this study did this in the HC group. The larger study consisted of a respiratory challenge test, a five-minute baseline HRV measurement, a long stress test and a short stress test. Only the results of the long stress test are reported here. The following parameters were measured: blood pressure, PetCO₂, HR, HRV, skin conductance, peripheral skin temperature, respiration and muscle tension (M. Trapezius). This study focuses only on the parameter HR.

3.3. Procedure

The stress test began with a baseline measurement of two minutes and was followed by three stressors of two minutes each. The Stroop color word task was the first stressor. Words describing a color were shown (“red”, “yellow”, “blue” or “green”) while these words were printed in a different color. The subjects had to name the print color of the word and ignore the word itself, and this had to be done as quickly and accurately as possible. Speed and accuracy were not measured, but the intention was to provoke the ASR. If an error was made, it was reported to the subject. If participants did not make a lot of mistakes, the experimenter prompted them to go faster.

After the first stressor, the remainder of the stress test was performed with the eyes closed. The second stressor consisted of the Mental Arithmetic Task (MAT), where the participants

had to continuously subtract the number seven, starting from the number 1081. The number had to be said out loud and this had to be done as quickly as possible. When an incorrect answer was given, the participant needed to start over.

The third stressor was a stress talk, in which the subjects had to talk about a stressful experience and describe their thoughts and feelings during this stressful experience.

A recovery period of two minutes followed each stressor. During these recovery periods participants were asked to close their eyes and relaxing music was played. The duration of the stress test was 15 minutes in total. HR was measured continuously.

Measurements were standardized by performing the test from the same starting position. The subjects sat on a chair with their feet on the ground and their hands in their lap. During baseline measurements, subjects were asked not to speak and to sit still.

3.4. Outcome measures

The primary outcome measures were HR and HR slope. HR was measured at 32 Hz with the MindMedia NeXus 10 by a photoplethysmogram (PPG) sensor attached to one finger of the non-dominant hand.

3.5. Statistical analyses

The stress test consisted of seven phases: baseline, stressor 1, recovery 1, stressor 2, recovery 2, stressor 3 and recovery 3. For each phase, the average HR was calculated for every 30 seconds (four time segments per phase). For each dependent variable, random intercept random slope linear mixed model analyses were performed on the seven different phases to investigate between-group differences. Group (between-subject, five levels: FM/CFS, burnout, overstrain, PD and HC) and time (within-subject, four levels) were used as independent variables. In case of a main effect of group, post-hoc multiple comparisons were performed with Tukey-Kramer correction for multiple testing. A priori specific contrasts in the time*group interaction effect were performed to investigate hypotheses about the evolution of HR in each phase: 1) all patients vs. controls, 2) PD vs. MUPS, 3) overstrain vs. burnout, 4) overstrain vs. FM/CFS, 5) burnout vs. FM/CFS and 6) PD vs. HC. The subgroup patients

consisted of overstrain, burnout, FM/CFS and PD. The MUPS group included overstrain, burnout and FM/CFS. All statistical analyses were performed in SAS 9.4..

4. Results

4.1. Sample characteristics

The initial study sample consisted of 105 patients (26 FM/CFS, 35 burnout, 24 overstrain and 20 PD) and 30 HC. HR data from one FM/CFS, two burnout, one overstrain and one HC could not be analyzed due to technical problems. There were also patients of which some data could not be used due to motion artifacts. An overview of all available data can be found in table 1. The final sample consisted of 101 patients (33 men) and 29 HC (9 men). A more detailed description of the age and gender within each group can be found in table 2.

Table 1

Available data for analysis in each phase, for each group

	<i>Baseline</i>	<i>ST1</i>	<i>RE1</i>	<i>ST2</i>	<i>RE2</i>	<i>ST3</i>	<i>RE3</i>
FM/CFS	25	22	25	21	25	20	25
Burnout	33	33	33	33	33	32	32
Overstrain	23	23	23	23	23	22	23
PD	20	18	20	19	20	18	20
HC	29	29	29	29	29	29	29

Number of participants with available data in each phase for each group. ST: stressor, RE: recovery, FM/CFS: fibromyalgia/chronic fatigue syndrome, PD: panic disorder, HC: healthy controls

Table 2

Demographic characteristics of participants

	<i>FM/CFS</i>	<i>Burnout</i>	<i>Overstrain</i>	<i>PD</i>	<i>HC</i>
Age (years)					
Mean (SD)	41.85 (9.37)	42.83 (8.67)	41.58 (10.08)	31.5 (10.31)	40.23 (9.63)
Range	22-58	25-59	25-58	18-62	20-58
Gender (%)					
Male	8	43	33	40	30
Female	92	57	67	60	70

SD: standard deviation, FM/CFS: fibromyalgia/chronic fatigue syndrome, PD: panic disorder, HC: healthy controls

4.2. Differences between patients and controls in each phase (figure 1)

4.2.1. Baseline

HR did not change significantly over time during baseline (main effect of time $F_{1,125} = .32$, $p = .57$). There was a significant difference in HR between groups at baseline (main effect of group $F_{4,260} = 4.87$, $p < .001$). Post-hoc tests revealed that the HC group had a significantly lower HR than the FM/CFS ($t_{260} = 3.58$, $p = .004$) and PD ($t_{260} = -3.63$, $p = .003$) groups. HR slope did not differ between groups at baseline (interaction effect time*group $F_{4,260} = 1.14$, $p = .34$).

4.2.2. Stressor 1: Stroop color word task

HR changed significantly over time during the first stressor (main effect of time $F_{1,120} = 9.40$, $p = .003$), with post-hoc tests indicating a significant decrease only in the overstrain ($t_{250} = -2.64$, $p = .009$) and HC ($t_{250} = -3.36$, $p < .001$) groups. A significant difference was found between groups (main effect of group $F_{4,250} = 2.77$, $p = .028$). HR of the FM/CFS group was overall significantly higher than the HC group ($t_{250} = 2.78$, $p = .046$). HR slope was different between groups (interaction effect time*group $F_{4,250} = 3.40$, $p = .010$). A significant difference was found between the overall patient group vs. controls ($t_{260} = -2.02$, $p = .045$) and overstrain vs. burnout ($t_{260} = -2.84$, $p = .005$). The HC group showed a steeper declining slope compared to patients. The slope of the overstrain group showed a significant steeper decline in HR compared to the burnout group.

4.2.3. Recovery 1

There was a significant difference between groups during the first recovery phase (main effect of group $F_{4,260} = 5.07$, $p < .001$). Post-hoc tests revealed that the HC group had a significantly lower HR than the FM/CFS ($t_{260} = 4.16$, $p < .001$) and PD ($t_{260} = -3.90$, $p = .001$) groups. No main effect of time ($F_{1,125} = 1.45$, $p = .23$), nor a time*group interaction effect ($F_{4,260} = 1.04$, $p = .38$) was found.

4.2.4. Stressor 2: MAT

There was a significant change in mean HR over time during the second stressor (main effect of time $F_{1,120} = 13.04$, $p < .001$). The mean HR decreased significantly over time in the patients ($t_{250} = -3.07$, $p = .002$) and HC ($t_{250} = -2.58$, $p = .010$) groups. No difference was found between

groups (main effect of group $F_{4,250} = 2.24, p = .07$), nor did HR slope differ between groups (time*group interaction effect $F_{4,250} = .87, p = .48$).

4.2.5. Recovery 2

During recovery 2 the mean HR changed significantly over time (main effect of time $F_{1,125} = 9.81, p = .002$) and there was a difference between groups (main effect of group $F_{4,260} = 5.03, p < .001$). A significant decrease in mean HR over the course of the recovery was found in the HC ($t_{260} = -2.13, p = .034$), patients ($t_{260} = -2.47, p = .014$) and MUPS ($t_{260} = -2.28, p = .024$) groups. Post-hoc tests revealed a significantly lower HR in the HC group compared to the FM/CFS ($t_{260} = 4.06, p < .001$) and PD ($t_{260} = -3.71, p = .002$). HR slope did not differ between groups (time*group interaction effect, $F_{4,260} = .27, p = .90$).

4.2.6. Stressor 3: stress talk

The mean HR changed significantly over time during stressor 3 (main effect of time $F_{1,116} = 29.48, p < .001$). A significant decrease in HR over time was found in the PD ($t_{242} = -3.38, p < .001$), HC ($t_{242} = -4.98, p < .001$), patients ($t_{242} = -3.75, p < .001$) and MUPS ($t_{242} = -2.26, p = .025$) groups. There were no differences between groups for mean HR (main effect of group $F_{4,242} = 1.53, p = .19$), but a difference in HR slope was found (time*group interaction effect $F_{4,242} = 2.89, p = .023$). The slope of time was significantly different in patients vs. controls ($t_{242} = -2.45, p = .015$) and panic vs. MUPS ($t_{242} = -2.01, p = .046$). The HC group showed a steeper decline in HR compared to the overall patient group and the MUPS group had a steeper decline in HR than the panic group.

4.2.7. Recovery 3

HR did not change significantly over time (main effect of time $F_{1,124} = 1.31, p = .25$). A difference in mean HR was found between groups (main effect of group $F_{4,258} = 4.11, p = .003$). Post-hoc tests revealed a significantly lower HR in the HC group compared to the FM/CFS ($t_{258} = 3.89, p = .001$) and PD ($t_{258} = -3.27, p = .011$) groups. HR slope did not differ between groups (time*group interaction effect $F_{4,258} = .58, p = .67$).

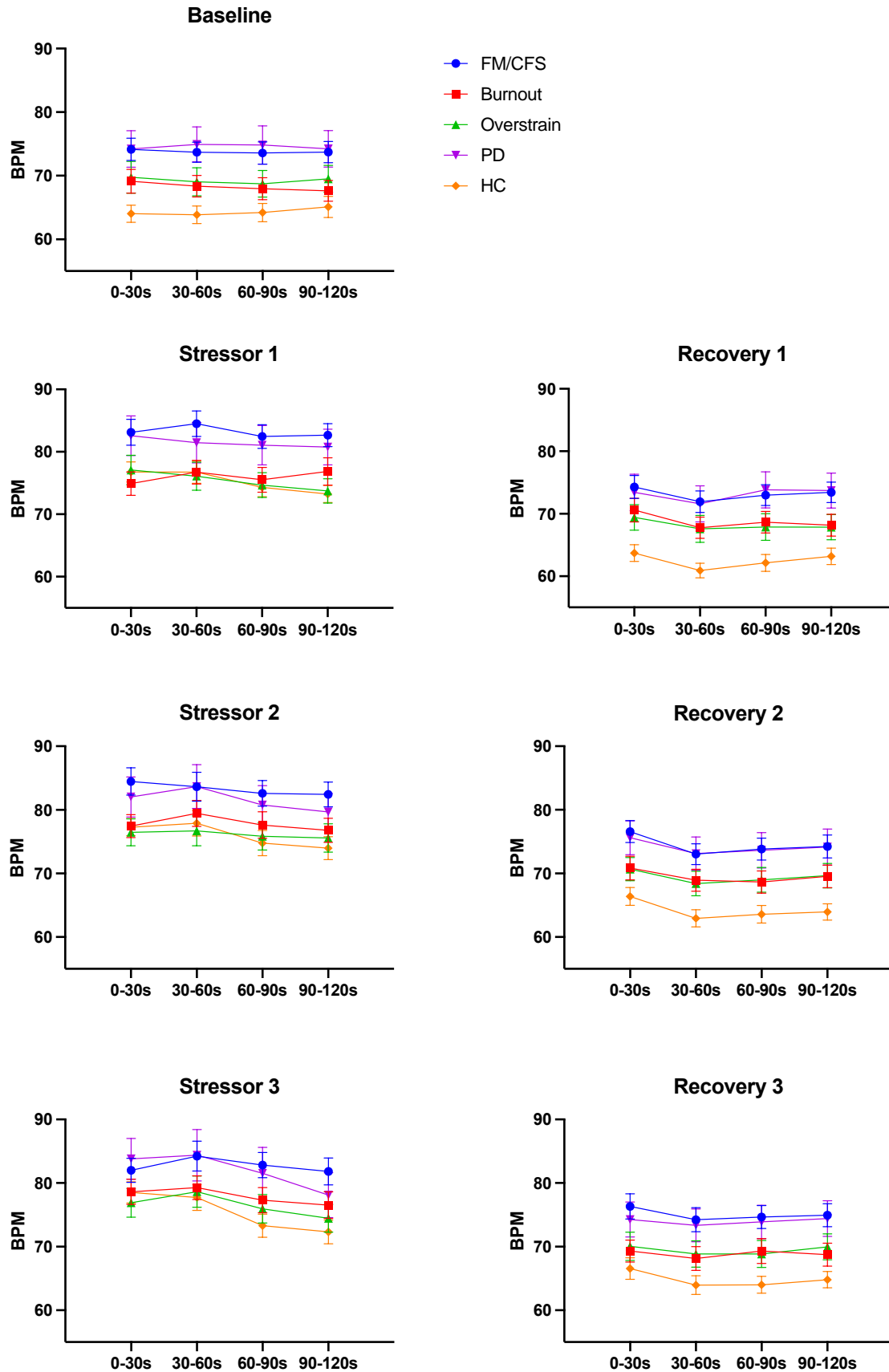


Figure 1: Mean HR in beats per minute (BPM) during the baseline, stressor and recovery phase.

5. Discussion

The aim of this study was to investigate HR in patients with MUPS (overstrain, burnout and FM/CFS) and compare this with the HR of patients with PD and HC. HR was examined at baseline, during various stressors and during recovery. There are similarities in physical complaints between the patient groups, but little research has been done comparing ASR in these groups. A higher HR was found in the FM/CFS group compared to HC during the baseline and recovery periods, suggesting a predominance of the sympathetic nervous system. The same results were found in the PD group compared to the HC group. The overall patient group habituated slower to the Stroop color word task and the stress talk compared to HC.

We would expect an increase in HR during the stressors in patients and HC, but we found a significant decrease in HR over time during all stressors. However, in the graphs we can see an initial increase in HR followed by a decrease, contrary to our first hypothesis where we expected a steeper incline of HR and higher HR values during the stressors in patients compared to HC. The negative slope indicates how quickly HR habituated to the stressor. We found that the HC group had a steeper decline in HR compared to patients during the Stroop color word task and the stress talk, indicating that the HC habituated faster to the stressors than the patients. This is in contrast to the study of Fauvel et al. (2000), which found that HR increased significantly during mental stress talks (as in the third stressor) in healthy individuals.

During the baseline and recovery periods we did find a higher HR in the FM/CFS and PD groups compared to the HC. This is in line with previous findings, which found an increased autonomic activity at rest in FM patients (Martínez-Lavín & Hermosillo, 2000; Matías Pompa, López López, Alonso Fernández, Vargas Moreno, & González Gutiérrez, 2020). However, these studies also found a decreased autonomic activity during stressors, just like in the study of Chalaye, Lafrenaye, Goffaux, and Marchand (2014), which we could not demonstrate in this study. With regard to PD, Blechert, Michael, Grossman, Lajtman, and Wilhelm (2007) did not find a clearly different autonomic pattern compared to HC, both during baseline and during a stressor.

No evidence was found to support our hypothesis about ASR in disorders on the left of the stress continuum being more disturbed than FSS presumed to be located on the right. No significant differences were found when comparing both groups with each other, thus there is no significant difference in ASR between these groups. The fact that some patients do

develop FSS, suggests that other processes play a role in the development. We hypothesize that central processes, such as interoception and symptom perception, are an important factor in this. The research of de Looft, Cornet, Embregts, Nijman, and Didden (2018) was unable to form a definitive conclusion about the psychophysiological measurements in burnout patients.

Because of the similar physical symptoms between MUPS and PD, we also explored if there was a difference between these groups. No differences were found in HR between the MUPS and PD groups. However, during the stress talk HR of the MUPS showed a steeper decline compared to the PD group, indicating that the MUPS group habituated more quickly to the stressor. FSS seem to be most similar to the PD group as both showed a significantly higher HR during the baseline and recovery phases of the stress test.

Various stressors were used in this study, this must be taken into consideration in the analysis of the results. We did not find any significant results during the MAT. We suggest that the MAT was less stressful than the other stressors. The stress talk could be seen as more stressful than the MAT, because subjects were talking about an individual stressful experience. Some subjects might have perceived the MAT as less stressful than the other stressors depending on their math skills.

This study has some limitations that must be taken into account when analyzing the results. A first limitation is the use of an observational design, which means that we could not determine causalities. Furthermore, no covariates were used in the analysis, such as medication, alcohol and tobacco use, income and parental education. The use of antidepressants could have an influence (bradycardia or tachycardia) on HR (Spindelegger et al., 2015). This is important in the patient groups, because the HC group did not take any psychotropic medication. The frequent use of tobacco and alcohol may cause a hypo-arousal of the ANS during stress. Lower HR was found during stress in people consuming a high number of alcoholic drinks per week. Frequent smokers showed blunted HR reactivity to stress (Evans et al., 2012). McGrath, Matthews, and Brady (2006) found the higher the income and the more years of parental education, the lower the HR. Finally, there was no standardization for the influence of the menstrual cycle, this can also be a reason for inconsistent results as anxiety provoking stimuli might exacerbate ASR premenstrual (Nillni, Toufexis, & Rohan, 2011). Armbruster, Grage,

Kirschbaum, and Strobel (2018) also suggested a temporary shift in the ANS towards a more fear-and-anxiety-prone affective state in the luteal phase due to a higher HR.

A strength of this study was that we looked at HR in detail in seven different phases (baseline, three stressors and three recovery phases).

A better understanding of the profile of the different MUPS disorders and their underlying mechanisms, like abnormalities in HR, can lead to more specific treatment plans. HR biofeedback could be used to make patients more aware of their HR and help them to regulate it better. If patients succeed in consciously regulating their HR it may have a positive influence on the symptoms they experience. HR profile may also contribute to the diagnostic process in the future.

In general, we found some evidence for a dysregulation of the ASR in patients compared to HC, because patients habituated slower to the various stressors than HC. We did not find a difference in ASR between patients with MUPS and PD. The FM/CFS group seems to be most similar to the PD group, because both of these groups had a higher HR during baseline and recovery periods compared to HC.

In future research it would be interesting to look at shorter time frames of the stressors, to investigate the initial HR response before habituation to the stressors take place. Factors like medication, the use of tobacco and alcohol, income and parental education should also be taken into account in the statistical analysis. Future research should also standardize for the influence of the menstrual cycle. Other parameters of the ANS must also be considered, to get a broader picture of the ASR in the different patient groups and the HC. As no difference was found between overstrain/burnout compared to FSS patients, it is important to investigate the role of central processes in the development of FSS.

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APPENDICES



Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - INFORMATION STUDENT

Faculteit/School: **Faculteit Revalidatiewetenschappen**

Faculty/School: **Rehabilitation Sciences**

Stamnummer + naam: **1643170 De Wit Aline**

Student number + name

Opleiding/Programme: **2 ma revalid. & kine kinderen**

INSTRUCTIES - INSTRUCTIONS

Neem onderstaande informatie grondig door.

Print dit document en vul het aan met DRUKLETTERS.

In tijden van van online onderwijs door COVID-19 verstuurt u het document (scan of leesbare foto) ingevuld via mail naar je promotor. Je promotor bezorgt het aan de juiste dienst voor verdere afhandeling.

Vul luik A aan. Bezorg het formulier aan je promotoren voor de aanvullingen in luik B. Zorg dat het formulier ondertekend en gedateerd wordt door jezelf en je promotoren in luik D en dien het in bij de juiste dienst volgens de afspraken in jouw opleiding.

Zonder dit inschrijvingsformulier krijg je geen toegang tot upload/verdediging van je masterproef.

Please read the information below carefully.

Print this document and complete it by hand writing, using CAPITAL LETTERS.

In times of COVID-19 and during the online courses you send the document (scan or readable photo) by email to your supervisor. Your supervisor delivers the document to the appropriate department.

Fill out part A. Send the form to your supervisors for the additions in part B. Make sure that the form is signed and dated by yourself and your supervisors in part D and submit it to the appropriate department in accordance with the agreements in your study programme.

Without this registration form, you will not have access to the upload/defense of your master's thesis.

LUIK A - VERPLICHT - IN TE VULLEN DOOR DE STUDENT PART A - MANDATORY - TO BE FILLED OUT BY THE STUDENT

Titel van Masterproef/Title of Master's thesis:

behouden - keep

wijzigen - change to:

AUTONOMIC STRESS REACTIVITY IN MEDICALLY UNEXPLAINED PHYSICAL SYMPTOMS

/:

behouden - keep

wijzigen - change to: **COMPARISON WITH PANIC DISORDER PATIENTS AND HEALTHY CONTROLS**

In geval van samenwerking tussen studenten, naam van de medestudent(en)/In case of group work, name of fellow student(s):

behouden - keep

wijzigen - change to:

LUIK B - VERPLICHT - IN TE VULLEN DOOR DE PROMOTOR(EN)
PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

Wijziging gegevens masterproef in luik A/Change information Master's thesis in part A:

goedgekeurd - approved

goedgekeurd mits wijziging van - approved if modification of:

Scriptie/Thesis:

openbaar (beschikbaar in de document server van de universiteit) - public (available in document server of university)

vertrouwelijk (niet beschikbaar in de document server van de universiteit) - confidential (not available in document server of university)

Juryverdediging/Jury Defense:

De promotor(en) geeft (geven) de student(en) het niet-bindend advies om de bovenvermelde masterproef in de bovenvermelde periode/The supervisor(s) give(s) the student(s) the non-binding advice:

te verdedigen/to defend the aforementioned Master's thesis within the aforementioned period of time

de verdediging is openbaar/in public

de verdediging is niet openbaar/not in public

niet te verdedigen/not to defend the aforementioned Master's thesis within the aforementioned period of time

LUIK C - OPTIONEEL - IN TE VULLEN DOOR STUDENT, alleen als hij luik B wil overrulen
PART C - OPTIONAL - TO BE FILLED OUT BY THE STUDENT, only if he wants to overrule part B


In tegenstelling tot het niet-bindend advies van de promotor(en) wenst de student de bovenvermelde masterproef in de bovenvermelde periode/In contrast to the non-binding advice put forward by the supervisor(s), the student wishes:

niet te verdedigen/not to defend the aforementioned Master's thesis within the aforementioned period of time

te verdedigen/to defend the aforementioned Master's thesis within the aforementioned period of time

LUIK D - VERPLICHT - IN TE VULLEN DOOR DE STUDENT EN DE PROMOTOR(EN)
PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)


27/05/2021

Datum en handtekening promotor(en)
Date and signature supervisor(s)



28/05/2021



Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - INFORMATION STUDENT

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: Rehabilitation Sciences

Stamnummer + naam: **1643134 Gielen Amber**
Student number + name

Opleiding/Programme: **2 ma revalid. & kine kinderen**

INSTRUCTIES - INSTRUCTIONS

Neem onderstaande informatie grondig door.

Print dit document en vul het aan met DRUKLETTERS.

In tijden van van online onderwijs door COVID-19 verstuur je het document (scan of leesbare foto) ingevuld via mail naar je promotor. Je promotor bezorgt het aan de juiste dienst voor verdere afhandeling.

Vul luik A aan. Bezorg het formulier aan je promotoren voor de aanvullingen in luik B. Zorg dat het formulier ondertekend en gedateerd wordt door jezelf en je promotoren in luik D en dien het in bij de juiste dienst volgens de afspraken in jouw opleiding.

Zonder dit inschrijvingsformulier krijg je geen toegang tot upload/verdediging van je masterproef.

Please read the information below carefully.

Print this document and complete it by hand writing, using CAPITAL LETTERS.

In times of COVID-19 and during the online courses you send the document (scan or readable photo) by email to your supervisor. Your supervisor delivers the document to the appropriate department.

Fill out part A. Send the form to your supervisors for the additions in part B. Make sure that the form is signed and dated by yourself and your supervisors in part D and submit it to the appropriate department in accordance with the agreements in your study programme.

Without this registration form, you will not have access to the upload/defense of your master's thesis.

LUIK A - VERPLICHT - IN TE VULLEN DOOR DE STUDENT PART A - MANDATORY - TO BE FILLED OUT BY THE STUDENT

Titel van Masterproef/Title of Master's thesis:

behouden - keep

wijzigen - change to: **AUTONOMIC STRESS REACTIVITY IN MEDICALLY UNEXPLAINED PHYSICAL SYMPTOMS**

/:

<input type="radio"/> behouden - keep
<input checked="" type="radio"/> wijzigen - change to: COMPARISON WITH PANEC DISORDER PATIENTS AND HEALTHY CONTROLS

In geval van samenwerking tussen studenten, naam van de medestudent(en)/In case of group work, name of fellow student(s):

<input checked="" type="radio"/> behouden - keep
<input type="radio"/> wijzigen - change to:

LUIK B - VERPLICHT - IN TE VULLEN DOOR DE PROMOTOR(EN)
PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

Wijziging gegevens masterproef in luik A/Change information Master's thesis in part A:

<input checked="" type="radio"/> goedgekeurd - approved
<input type="radio"/> goedgekeurd mits wijziging van - approved if modification of:

Scriptie/Thesis:

<input checked="" type="radio"/> openbaar (beschikbaar in de document server van de universiteit)- public (available in document server of university)
<input type="radio"/> vertrouwelijk (niet beschikbaar in de document server van de universiteit) - confidential (not available in document server of university)

Juryverdediging/Jury Defense:

De promotor(en) geeft (geven) de student(en) het niet-bindend advies om de bovenvermelde masterproef in de bovenvermelde periode/The supervisor(s) give(s) the student(s) the non-binding advice:

<input checked="" type="radio"/> te verdedigen/to defend the aforementioned Master's thesis within the aforementioned period of time
<input checked="" type="radio"/> de verdediging is openbaar/in public
<input type="radio"/> de verdediging is niet openbaar/not in public
<input type="radio"/> niet te verdedigen/not to defend the aforementioned Master's thesis within the aforementioned period of time

LUIK C - OPTIONEEL - IN TE VULLEN DOOR STUDENT, alleen als hij luik B wil overrulen
PART C - OPTIONAL - TO BE FILLED OUT BY THE STUDENT, only if he wants to overrule part B

In tegenstelling tot het niet-bindend advies van de promotor(en) wenst de student de bovenvermelde masterproef in de bovenvermelde periode/In contrast to the non-binding advice put forward by the supervisor(s), the student wishes:

<input type="radio"/> niet te verdedigen/not to defend the aforementioned Master's thesis within the aforementioned period of time
<input type="radio"/> te verdedigen/to defend the aforementioned Master's thesis within the aforementioned period of time

LUIK D - VERPLICHT - IN TE VULLEN DOOR DE STUDENT EN DE PROMOTOR(EN)
PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)

Date and signature student(s)

27/05/2021



Datum en handtekening promotor(en)

Date and signature supervisor(s)

28/05/2021



Inschrijvingsformulieren MP2 Inbox x



Amber Gielen

vr 28 mei 09:11 (10 dagen geleden)



Beste mevrouw Van Den Houte, In bijlage kan u de inschrijvingsformulieren van Aline en mezelf en het...



Maaïke VAN DEN HOUTE

vr 28 mei 14:25 (10 dagen geleden)



aan Amber, mij, Katleen, Indra ▾

Beste Amber en Aline,

In bijlage kunnen jullie de ingevulde en ondertekende documenten terugvinden.
Bij deze geef ik jullie ook toestemming om de masterproef in te dienen en te verdedigen.

Vriendelijke groeten,

Maaïke

Op vr 28 mei 2021 om 09:11 schreef Amber Gielen <amber.gielen@student.uhasselt.be>:



--

Dr. Maaïke Van Den Houte

Tijdelijk Academisch Medewerker

T 016 / 37.46.95

[UHasselt - onderzoeksgroep gezondheidspsychologie](#)

www.uhasselt.be

Universiteit Hasselt - Campus Diepenbeek
Agoralaan Gebouw A - B-3590 Diepenbeek

Op za 5 jun. 2021 om 18:53 schreef Amber Gielen <amber.gielen@student.uhasselt.be>:

Beste mevrouw Vanhille,

Er is op het laatste moment door onze promotor nog een verandering doorgevoerd aan de titel van onze masterproef. De correcte titel is: "Autonomic stress reactivity in patients with medically unexplained physical symptoms". De andere gegevens zijn correct.

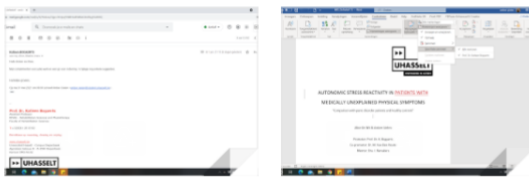
Met vriendelijke groeten,

Amber Gielen
1643134

Op vr 4 jun. 2021 om 11:52 schreef Vicky VANHILLE <vicky.vanhille@uhasselt.be>:

...

2 bijlagen



Katleen BOGAERTS

aan Vicky, Amber, mij ▾

12:29 (11 minuten geleden)



Dag allen,

Hierbij mijn akkoord voor aanpassing van de titel.

Hartelijke groeten,

...

--

Prof. Dr. Katleen Bogaerts

Assistant Professor

REVAL - Rehabilitation Sciences and Physiotherapy

Faculty of Rehabilitation Sciences

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): Aline De Wit Datum: 28/05/2021
Titel Masterproef: Autonomic stress reactivity in medically unexplained physical symptoms

- 1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
- NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
 - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
 - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
 - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
 - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
 - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	0	0	0	0	X	0
Methodologische uitwerking	X	0	0	0	0	0
Data acquisitie	X	0	0	0	0	0
Data management	0	0	0	0	X	0
Dataverwerking/Statistiek	0	0	0	0	X	0
Rapportage	0	0	0	X	0	0

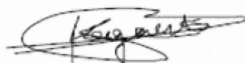
- 2) Niet-bindend advies: Student(e) krijgt toelating/~~geen toelating~~ (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.
- 3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) openbaar verdedigd worden.
- 4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening
Student(e)


28/05/2021

Datum en handtekening
promotor(en)

28/05/2021



Datum en handtekening
Co-promotor(en)

28/05/2021



In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:


Naam Student(e): Amber Gielen Datum: 28/05/2021
Titel Masterproef: Autonomic stress reactivity in medically unexplained physical symptoms

- 1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
- NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
 - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
 - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
 - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
 - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
 - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	0	0	0	0	X	0
Methodologische uitwerking	X	0	0	0	0	0
Data acquisitie	X	0	0	0	0	0
Data management	0	0	0	0	X	0
Dataverwerking/Statistiek	0	0	0	0	X	0
Rapportage	0	0	0	X	0	0

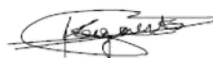
- 2) Niet-bindend advies: Student(e) krijgt toelating/~~toelating~~ (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.
- 3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) openbaar verdedigd worden.
- 4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening
Student(e)

28/05/2021


Datum en handtekening
promotor(en)

28/05/2021



Datum en handtekening
Co-promotor(en)

28/05/2021

