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Modulation of startle and heart rate responses by fear of physical activity in patients with heart failure and in healthy adults

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ABSTRACT

Fear of physical activity (FoPA) has been suggested as a barrier to physical activity in patients with heart failure and might be associated with low adherence to exercise regimen despite medical guideline recommendations. The present study examined physiological indicators of FoPA by assessing startle modulation (via EMG at the orbicularis oculi muscle) and heart rate responses (derived from ECG) after affective priming with lexical stimuli of positive, neutral, and negative valence, as well as words related to physical activity as potentially phobic cues. After screening for FoPA in patients with heart failure and healthy adults, twenty participants each were assigned to one of three subsamples: a healthy control group and two cardiac patient groups scoring either low or high on FoPA. The high-FoPA group showed startle potentiation and more pronounced heart rate acceleration (than did controls) in the phobic prime condition, indicating defensive response mobilization. Among the patients, higher FoPA accounted for 30% of the startle potentiation by phobic priming, whereas general anxiety, depression, and disease severity were no significant predictors of startle modulation. These findings suggest that FoPA in patients with heart failure is associated with defensive responses on a physiological level that might be indicative of avoidance behavior, thereby contributing to low adherence to exercise regimen. Thus, FoPA presents a significant target for psychological interventions to foster physical activity in cardiac patients.

1. Introduction

Heart failure shows rising prevalence rates in the population aged 50+, a lifetime risk of 33% for men and 28% for women at the age of 55 years, and 35% survival rate five years after the first diagnosis [1,2]. The pathophysiological syndrome is defined by reduced cardiac output or elevated intra-cardiac pressure, and characterized by symptoms such as breathlessness on exertion, reduced exercise tolerance, and increased time to recover after exercise [3]. Although heart failure treatment guidelines strongly recommend regular exercise to improve exercise capacity in terms of peak oxygen consumption and cardiac output [3], there is a lack of interventions that focus on psychological barriers to physical activity in those patients who show low adherence to exercise regimens due to symptom burden [4,5]. Differences between patients' strategies to emotionally cope with heart failure might contribute to either low or high levels of physical activity, as suggested by interview data [6]: Patients who reported to be physically active used *disavowal* of emotional strain as a coping strategy, whereas patients who showed low adherence to treatments used *avoidance* of unfavorable situations as a maladaptive coping strategy to reduce affective arousal due to anxiety. Since general anxiety has been shown to be unrelated to physical activity behavior in patients with heart failure, a specific fear of physical activity (FoPA) has been implicated to act as a barrier to physical activity in these patients [7].

To develop effective interventions fostering physical activity, basic research should focus on FoPA as a potential barrier to physical activity in terms of cognition, behavior, and physiology [8]. We developed the stimulus-response questionnaire Fear of Activity in Situations – Heart Failure (FActS-HF) to assess FoPA via self-report to situational descriptions depicting physical activity, addressing the affective and cognitive level [9]. Using this questionnaire, we recently showed that scores on the FActS-HF were negatively associated with accelerometer-

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based measures of physical activity behavior in patients with heart failure, e.g., less stair climbing and walking uphill [10]. While these findings support the validity of self-reported FoPA with regard to physical activity behavior, little is known about physiological reactions to arousing situations of physical activity, and in particular, arousal regulation mechanisms underlying high vs. low FoPA that might reflect different coping strategies for managing the burden of heart failure symptoms during physical activity.

The affective modulation paradigm provides an experimental approach to assess physiological reactions to emotional cues, such as potentially phobic situations of physical activity. These emotional stimuli activate specific motivational systems that are instantiated in subcortical-limbic brain structures in order to prepare the organism for adaptive responses (i.e., motivational priming) [11]. As primary physiological measure serves the experimentally elicited (i.e., probed) startle reflex, which is a defensive reaction to sudden threat and which varies in intensity depending on affective arousal by motivational priming. Thus, startle responsivity is a function of affective processing of emotional foreground stimuli.

In experiments based on the affective modulation paradigm, visual stimuli presented in the context of film or picture viewing or text-driven imagery are commonly employed to induce certain emotions (e.g. [12-14]). When aversive or pleasant pictures as foreground stimuli are probed in healthy, young volunteers, a robust pattern of startle potentiation or attenuation (relative to neutral stimuli) has been found, respectively [15]. In the case of text-driven imagery, perceptual processing of lexical stimuli is supplemented by additional memory-based processing, e.g., reading the word “fitness” and retrieving personal memories associated with physical activity [11]. If highly arousing pleasant imagery is probed, the deep processing of such content might be interrupted, which leads to startle potentiation and cardiac acceleration rather than startle attenuation and cardiac deceleration as observed in shallow processing during picture viewing [16,17]. Similarly, enhanced startle due to an attentional positivity bias has been found in older adults and linked to relatively enhanced processing of positive stimuli (as opposed by enhanced processing of negative stimuli in younger individuals) [18].

The affective modulation paradigm is largely based on a two-dimensional model of emotion, describing emotions as action dispositions in terms of activation of either appetitive or defensive motivation (i.e., affective valence), and the degree of motivational activation (i.e., arousal) [19]. Unpleasant stimuli activate the defensive motivational system, whereas pleasant stimuli prime the appetitive motivational system [15]. The emotional valence of both unpleasant and pleasant stimuli is processed in the amygdala, and only pleasant words seem to additionally involve the reward system of the brain, i.e., the mesolimibic dopamine system including the nucleus accumbens [11]. Threat-related stimuli activate the defensive motivational system to a higher degree (compared with the activation by common unpleasant stimuli) and thereby elicit an intense state of physiological arousal (i.e., fear) by sympathetic activation [20]. For instance, if phobic individuals are exposed to their feared object, they react with a potentiation of the startle reflex and heart rate (HR) acceleration compared with those reactions in non-phobic individuals [15]. Hence, defensive responsiveness, such as reflex facilitation and tachycardia, suggests the activation of a fear network involving the amygdala with its projections to hypothalamic and brainstem areas that regulate autonomic nervous system responses [21, 22]. Fear-potentiated startle responses are mediated by the amygdala, in contrast to anxiety responses that are mediated by a distinct neural system, i.e., the bed nucleus of the stria terminalis, which is independent from startle circuitries [23].

Startle circuitries have been experimentally examined using different types of startle probes, such as bursts of loud noise and high-pressure air puffs [24]. Even though the acoustic startle circuit has been studied more extensively than the tactile one, findings indicate that both acoustic and tactile startle responses are initiated in the pontine reticular formation and generated by shared motor systems [25]. It has been proposed that the involved pathways to the nucleus reticularis pontis caudalis differ between tactile and acoustically evoked startle responses, namely the trigeminal and the cochlear nerve, respectively [26]. In the trigeminal pathway, cutaneous stimuli, such as air puffs on the temples area, are detected by skin mechanoreceptors that transmit sensory information to the ophthalamic branch of the trigeminal nerve [25]. Trigeminal neurons activate giant neurons in the pontine reticular formation, whose axons project, i.a., onto motoneurons of the N. facialis that activate the eye blink component of the startle response [26,27]. If individuals with high FoPA are stimulated by specific emotional stimuli reminiscent of situations of physical activity, it is plausible to assume that circuitries mediating affective arousal are more strongly activated compared with those in individuals reporting low FoPA.

The overall purpose of the present study was to examine physiological indicators of FoPA by assessing affective modulation of startle and HR responses after priming with lexical stimuli. To the best of our knowledge, the affective startle paradigm has never been applied in cardiac patients. Since heart failure often develops with higher age, this might affect the activation of subcortical-limbic brain structures and, therefore, the pattern of startle response modulation. Thus, we limited the present study to individuals aged 50+ to keep the positivity bias constant, and used air puffs instead of acoustic probes to elicit startle responses because we anticipated hearing deficits especially in elderly participants. The first aim was to validate the a-priori assignment of lexical stimuli to valence prime conditions based on the participants' valence ratings, and to evaluate startle modulation by emotional words. We expected no startle response attenuation after priming with positive imagery, but potentiated startle responses after priming with negative material. The second aim was to investigate whether the confrontation with physical activity-related words leads to startle potentiation in individuals with high FoPA, and whether this association was independent of general anxiety, depression, and medical variables. The third aim was to compare HR responses to emotional words, in particular those related to physical activity, between patients scoring either high or low on FoPA and healthy controls.

2. Method

2.1. Participants

Participants were selected based on a FoPA screening of 114 patients diagnosed with heart failure and 60 healthy adults ≥ 50 years of age. Full inclusion criteria of patients with heart failure are provided elsewhere (ClinicalTrials.gov Identifier: NCT03119298). For the purpose of the present study, we defined healthy as absence of cardiovascular disease or other severe diseases that impair physical activity (e.g., advanced stages of cancer). As the FActS scores differed significantly between men (Mdn = 3, coding = 0) and women (Mdn = 2, coding = 1) on a scale from 0 (= low) to 5 (= high), $t(112) = -3.3$, $p = 0.001$, a sex-specific median-split was applied to divide the patient screening sample into two groups scoring either low or high on FoPA [28]. Finally, individuals from the split patient screening samples and the healthy screening sample were matched on a case-by-case basis on sex and age until 20 participants were assigned to each of three study groups: the high-FoPA, low-FoPA, and healthy control group.

The total sample comprised 60 participants split into three groups with 13 men and 7 women each. Age ranged between 54 and 82 years ($M = 66.0 \pm 7.6$) and was statistically equivalent between the high-FoPA, low-FoPA, and healthy group with 65.9, 65.7, and 66.4 years, respectively (see Table 1), reflecting the matching procedure. The sample size was planned a-priori for a 3 (groups) × 4 (repeated measurement levels) design using the software G*Power [29]. We entered the parameters $\alpha = 0.05$, $1\text{-}\beta = 0.90$, and set the effect size on a moderate level of $f = 0.2$ resulting in a required sample size of n = 57.

Table 1
Participant characteristics of healthy controls and patients with heart failure scoring either low or high on fear of physical activity (N = 60).

M ± SD	Healthy controls (1)	Patients with low FoPA (2)	Patients with high FoPA (3)	*p*-value	Post-hoc
Age (in years)	66.4 ± 7.6	65.7 ± 7.7	65.9 ± 8.0	0.959	
Female sex[a],%	35.0	35.0	35.0	> 0.999	
Body mass index	24.7 ± 3.7	28.6 ± 4.6	27.4 ± 4.1	0.012	(2 vs. 1)
≥ 9 years of education[a],%	94.7[1]	52.6[1]	20.0	< 0.001	(1 vs. 2 vs. 3)
Married[a],%	60.0	80.0	80.0	0.296	
Hospitalization (past 12 months)[a],%	15.8[1]	40.0	65.0	0.008	(3 vs. 1)
Non-cardiovascular morbidity[a],%	35.0	50.0	70.0	0.101	
LVEF,%	NA	37.9 ± 13.5	29.7 ± 8.0[1]	0.028	
Blood Pressure (in mmHG)					
Systolic	NA	123.4 ± 20.6[2]	130.4 ± 18.4	0.283	
Diastolic	NA	74.0 ± 9.5[2]	81.3 ± 25.5	0.263	
ICD[a],%	NA	85.0	95.0	0.605	
Medication[a],%					
Diuretics	NA	80.0	90.0	0.661	
ACE inhibitor	NA	45.0	60.0	0.527	
Angiotensin receptor blocker	NA	40.0	35.0	> 0.999	
Beta blocker	NA	75.0	85.0	0.695	
Antiarrhythmic agent	NA	30.0	25.0	> 0.999	
Antidepressant drug	NA	0.0	15.0	> 0.999	
STADI (1 = low; 4 = high)					
State Anxiety	NA	1.8 ± 0.5	2.3 ± 0.6	0.009	
State Depression	NA	1.8 ± 0.6	2.3 ± 0.6	0.020	
Trait Anxiety	NA	1.8 ± 0.5	2.2 ± 0.5	0.005	
Trait Depression	NA	1.8 ± 0.5	2.1 ± 0.6	0.046	
FActS(-HF) 15 (0 = low; 5 = high)	1.0 ± 1.0	1.3 ± 0.9	3.6 ± 0.8	< 0.001	(3 vs. 2/1)

[a] coding: 0 = male/no, 1 = female/yes; [1] superscript numbers indicate the number of missing values; abbreviations: FoPA = fear of physical activity; LVEF = left ventricular ejection fraction; ACE = Angiotensin converting enzyme; ICD = Implantable cardioverter defibrillator; STADI = State Trait Anxiety Depression Inventory; FActS(-HF) = Fear of Activity in Situations (– Heart Failure); NA = not applicable.

Although previous studies reported large effect sizes for startle modulation with lexical stimuli [11, 30], we decided to choose a more conservative estimation of effect size, and included one additional participant per group to compensate possible dropouts.

Ethical approval was obtained from the ethics committee of the Medical Association of the State of Rhineland-Palatinate / Germany (registration number: 837.465.16 / 10784). The experiment described in the present paper was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki).

2.2. Procedure

All participants were unaware of their experimental group assignment (single blinded) and underwent the same experimental procedure: after arrival at the laboratory, participants received both general written and oral information about the experiment entitled “Körperliche Aktivität und Gefühle” [physical activity and emotions], and signed a consent form. They were told that participation was voluntary and could be discontinued at any time. They were seated in a comfortable armchair in front of a 17-inch-monitor. Physiological sensors were attached, and participants were instructed in the use of the keyboard and to follow the information on the screen. After a five-minute adaption period, silencer headphones were put on with an integrated air puff device directed to the temples area, and weak background noise was presented to mask acoustic artifacts of the air puffs. The activation of the orbicularis oculi muscle was measured electromyographically (EMG) using two Ag/AgCl-electrodes (Tyco H124SG, diameter of 24 mm) placed under the left eye, one electrode in line with the pupil and the other electrode beneath lateral to the first one with an inter-electrode distance of approximately 25 mm [24]. HR was recorded electrocardiographically (ECG) using three Ag/AgCl-electrodes (Tyco H34SG) placed under the right collarbone and the left frontal and back pelvis (grounding system). EMG and ECG were recorded continuously during the experiment.

Participants were instructed to read carefully every word prompted on the screen and to ignore the intermittent air puffs near the eye. Initially, 12 air puffs were triggered to habituate participants' startle response and thereafter 80 words were presented in two blocks. Air puffs were randomly presented in 70% of trials during a randomized interval of 4 to 8 s after word onset, and after presenting an air puff, word offset was delayed for 1 s. Between each trial, a fixation cross was displayed for 1 s. After the first block of trials, a short break was included until the second block of word presentation was resumed initiated by 4 additional habituation air puffs. Afterwards, an unrelated experiment was conducted and subsequently the sensors and headphones were removed. The stimuli presented before were displayed once again on the screen, and participants rated the words' valence and arousal on a numeric rating scale from 1 (= low) to 10 (= high) that was visually supported by the Self-Assessment Manikin [31]. Finally, participants were debriefed on their experimental group assignment, received oral advice on physical activity, and were paid a monetary compensation (approximately 15€ per hour) for study participation.

2.3. Questionnaire measures and medical data

The sociodemographic questionnaire comprised questions on sex, birth date (age), body size and weight to calculate the body mass index (BMI = kg/m^2), and collected information on marital status, inpatient treatment during the last 12 months, level of education, and (co-) morbidities that impair physical activity. Patients additionally completed the Trait State Anxiety Depression Inventory (STADI) to assess anxiety and depression. The STADI trait and state subscales demonstrated satisfying internal consistencies (Cronbach's α = 0.76 and 0.80, respectively) in the patient screening sample. Patients' medical data, such as ICD-10 diagnoses, left ventricular ejection fraction (LVEF) as indicator of disease severity, medication intake, and implanted cardioverter defibrillator, were retrieved from medical records. Prior to experimental enrollment, healthy controls were interviewed via phone about their health status, specifically to rule out cardiovascular diseases.

The FActS-HF comprises 15 items describing everyday physical activities of moderate to vigorous intensity, which are rated on a scale from 0 (= low) to 5 (= high) in terms of both cognitive worries and feelings of tension. The FActS-HF provides stable measures (2 weeks test-retest coefficient $r = 0.81$) and there is evidence for its criterion validity, i.e., individuals with higher FActS-HF scores show lower levels of everyday physical activity as measured by accelerometer [9]. As the FActS-HF was developed for patients with heart failure, we adapted the questionnaire for use with healthy adults (i.e., FActS) by modifying heart failure-related parts of the instruction and some items (e.g., one question about "cardiac fitness group participation" was replaced by "fitness group participation"). The FActS was preliminarily validated in a sample of 116 volunteers aged ≥ 50 years [32]. Both the FActS-HF (Cronbach's $\alpha = 0.98$) and the adapted FActS ($\alpha = 0.97$) demonstrated a high degree of internal consistency in the screening samples.

2.4. Materials

The stimulus material comprised 80 German words extracted from the standardized *Berlin Affective Word List Reloaded* (BAWL-R) that provides representative ratings of valence and arousal for each word [33]. Selected words from the BAWL-R words were rated by four health scientists according to whether the words were related to physical activity or not, and expert concordance (i.e., ≥ 3 out of 4) served as criterion to assign each word either to the physical activity-related category (i.e., "phobic" word category) or unrelated word categories. As a result, 20 words were assigned to the phobic word category and 60 words were assigned either to the positive, neutral, or negative word category based on the BAWL-R valence ratings (see Appendix). The mean BAWL-R valence ratings of the positive, neutral, negative, and phobic word category were 2.2, 0.0, −1.6, and 0.9, respectively. Additionally, the four word categories were matched based on the BAWL-R validation norms with regard to arousal ratings, number of letters and syllables, and word frequency per one million words, all values: $F(3, 79) \leq 1.82$, $p \geq 0.110$. The mean BAWL-R arousal ratings of the positive, neutral, negative, and phobic word category were 2.8, 2.7, 3.0, and 2.7, respectively. The stimulus material was embedded in a script using the software E-Prime 2.0 (Psychology Software Tools, Inc.) and served as priming cues to modulate the startle response (see Appendix).

2.5. Data preprocessing

EMG data (recorded at 1000 Hz) was filtered (band-pass filter at 30–500 Hz), rectified, and integrated (within a time constant of 10 ms) using the software DasyLab (measX GmbH & Co. KG). The retrieved data was analyzed semi-automatically using the customized, C++-based program Clip 2.0 [34]. For each trial, EMG data were inspected for technical or physiological artifacts, and either manually corrected or discarded; non-responses were coded as zero when no peak could be detected. Startle response amplitudes were calculated by subtracting maximum peak (within a 20–200 ms interval after trigger onset) from baseline values (200 ms interval starting 250 ms prior to trigger onset). As zero values were included in individual averages, startle response magnitude was the final outcome measure. The reliability of EMG measures was estimated by correlating mean absolute magnitude (in μV) of the first trial block with that of the second block [35]. In the present sample, EMG measures demonstrated a satisfying (uncorrected split-half) reliability ($r_{tt} = 0.75$). In addition, reliabilities were estimated accordingly per valence category revealing the highest stability of EMG measures in the phobic prime condition ($r_{tt,positive} = 0.63$; $r_{tt,neutral} = 0.75$; $r_{tt,negative} = 0.61$; $r_{tt,phobic} = 0.86$).

ECG recordings were analyzed semi-automatically for R-waves in QRS-complexes using MATLAB 2019b (MathWorks, Inc.). Each trial was inspected for technical artifacts and premature heartbeats, and either manually corrected or rejected, if necessary. Inter-beat intervals were converted to instantaneous HR (i.e., from R-peak to R-peak) and averaged, weighted by fractions of real time [36]. Evoked changes in HR were calculated by subtracting mean HR across a pre-stimulus baseline of 1000 ms from average HR across intervals of 1500 ms during stimulus presentation. The peak acceleration (maximum ΔHR) during a 3 s intervall beginning 0.5 s after stimulus onset was calculated separately for each trial.

According to the criterion of ≥ 36% invalid trials, one participant (from the low-FoPA group) was excluded from the EMG analysis (i.e., > 20 missing out of 56 trials), and another participant (from the low-FoPA group) was excluded from the ECG analysis (i.e., > 26 out of 80 artefactual ECG trials). Prior to statistical analyses, ECG maximum ΔHR data was truncated by discarding responses above the 99.5th percentiles as outliers.

2.6. Statistical analysis

Baseline sample characteristics were calculated for the healthy control, low-FoPA, and high-FoPA group. Group differences in demographic, questionnaire, and medical data were determined using χ^2-tests for absolute frequencies of dichotomous variables, as well as *F*- and *t*-tests for continuous variables.

Repeated measures analyses of variance (rmANOVA) were performed to investigate effects of 4 *word categories* (within-subject factor: positive, neutral, negative, phobic) × 3 *groups* (between-subject factor: healthy control, low-FoPA, high-FoPA), as well as their interaction.[1] Greenhouse-Geisser-correction was applied, whenever appropriate. First, valence and arousal ratings served as separate dependent variables to validate the a-priori assignment of words to valence categories and the arousal matching between these categories. Second, startle response modulation by word categories was evaluated using the EMG raw magnitude as dependent variable. For further analysis of EMG data, raw magnitude was intra-individually standardized to control for inter-individual differences in startle responsivity [24], i.e., the individual mean of the neutral word category was subtracted from each value, and then divided by the individual standard deviation of the neutral category. Regression analysis was run involving all participants, with the FActS score being entered as independent variable and the standardized EMG magnitude in the phobic word category serving as dependent variable. Additionally, the regression analysis was repeated on data of the patient subsample only, controlling for LVEF, trait anxiety, and trait depression to estimate the proportion of variance explained by FoPA. Third, to test for peak HR acceleration, rmANOVA was run using maximum ΔHR as dependent variable. For all rmANOVAs, pairwise comparisons were performed using least significant differences to clarify main and interaction effects of the dependent variables (i.e., valence and arousal rating, startle response modulation, and peak HR acceleration). All statistical analyses were conducted using SPSS 26 (IBM Corp.) and the alpha level was set at $p < 0.05$.

3. Results

3.1. Participant characteristics

Table 1 presents demographic, psychometric and medical variables of the healthy control, low-FoPA, and high-FoPA group as well as statistical group comparisons for these variables.

Regarding demographic data, the three study subsamples were comparable with respect to age and sex, reflecting the matching procedure. The three groups differed significantly from each other in terms

[1] Note that additional rmANCOVAs including age as covariate were calculated, because the age range retained was still rather wide (i.e., 54-82 years) even though it did not differ between groups. However, the results reported in sections 3.3. and 3.4. were not affected by age: For both EMG and ECG data, the reported interactions of *word category* × *group* remained significant (both *ps* < 0.05), whereas no significant interaction of *word category* × *age* emerged (both *ps* s ≥ 0.187).

of education level, which was highest in the healthy group, followed by the low-FoPA group and lowest in the high-FoPA group. Furthermore, individuals in the healthy group had a significantly lower BMI compared with that of the low-FoPA group, and reported less frequent hospitalization in the past 12 months compared with that in the high-FoPA group.

Regarding questionnaire data, the high-FoPA group had higher FActS scores than the low-FoPA and healthy group, whereas the latter two groups had comparable FActS scores (Table 1). The FActS scores of the healthy group ranged from 0.0 to 3.4 (vs. 0.0 to 4.8 in the patient subsample). Scores of general anxiety and depression were consistently higher in the high-FoPA group compared with those of the low-FoPA group.

Regarding medical data, the two patient groups did not differ from each other except for LVEF, which was significantly lower in the high-FoPA group compared to the low-FoPA group, indicating a more severe heart failure condition. The numbers of implanted cardioverter defibrillator and medication intake were statistically equivalent between the patient groups.

3.2. Manipulation check

Table 2 presents the rating of the stimulus material involving all participants. RmANOVAs revealed significant main effects for word category on valence, $F(2.09,119.32) = 299.84$, $p < 0.001$, $\eta^2 = 0.84$, and arousal ratings, $F(2.02,115.34) = 21.14$, $p < 0.001$, $\eta^2 = 0.27$. Participants' ratings confirmed the a-priori assignment of the stimulus material to word valence categories (from positive over neutral to negative; see Table 2) based on the BAWL-R data. Furthermore, there was a significant interaction of *word category* × *group* for valence ratings, $F(4.19,119.32) = 6.85$, $p < 0.001$, $\eta^2 = 0.19$, but no interaction for arousal, $F(4.05,115.34) = 0.60$, $p = 0.665$, $\eta^2 = 0.02$. Post-hoc analyses of the interaction effect *word category* × *group* for valence ratings indicated that the healthy group rated higher valences for positive ($p = 0.003$) and phobic ($p < 0.001$) words compared with those ratings of the high-FoPA group. The healthy group reported also higher valence ratings of physical activity-related words compared with those of the low-FoPA group ($p = 0.003$).

Table 2
Ratings of stimulus material and physiological outcome measures of healthy controls and patients with heart failure scoring either low or high on fear of physical activity ($N = 60$).

M ± SD (by word category)	Healthy	Low-FoPA	High-FoPA
Valence rating (0 = low, 10 = high)			
positive	8.3 ± 0.6	7.9 ± 0.6	7.5 ± 1.2
neutral	5.7 ± 0.9	5.7 ± 0.7	5.4 ± 0.8
negative	3.0 ± 0.9	3.4 ± 1.3	3.6 ± 1.2
phobic	7.0 ± 0.9	6.0 ± 1.1	5.3 ± 1.3
Arousal rating (0 = low, 10 = high)			
positive	6.2 ± 1.8	5.7 ± 1.9	6.1 ± 1.5
neutral	4.8 ± 1.0	4.1 ± 1.6	4.7 ± 0.9
negative	5.9 ± 1.4	5.0 ± 1.5	5.1 ± 1.2
phobic	5.1 ± 1.3	4.4 ± 1.5	5.0 ± 1.1
EMG raw magnitude (in µV)		*n = 19*	
positive	115.7 ± 62.3	77.4 ± 45.7	82.8 ± 68.4
neutral	113.3 ± 60.7	80.9 ± 49.8	77.4 ± 66.7
negative	121.7 ± 65.1	76.7 ± 43.4	91.4 ± 81.2
phobic	115.1 ± 62.9	78.1 ± 48.6	89.7 ± 67.2
ECG peak HR acceleration (relative to baseline in bpm)		*n = 19*	
positive	1.3 ± 1.0	3.4 ± 3.4	4.0 ± 2.7
neutral	2.3 ± 3.3	2.6 ± 3.4	3.1 ± 2.3
negative	2.0 ± 2.9	2.5 ± 2.3	3.6 ± 2.3
phobic	1.6 ± 1.6	2.7 ± 2.3	3.6 ± 2.6

Abbreviations: FoPA = fear of physical activity; HR = heart rate.

For EMG startle magnitude, a main effect of *word category* was obtained, $F(2.5,140.9) = 2.88$, $p = 0.047$, $\eta^2 = 0.05$. Startle responses in the negative word category ($M = 96.6 \pm 8.5$) were statistically higher than those in both positive ($M = 92.0 \pm 7.8$; $p = 0.037$) and neutral ($M = 90.6 \pm 7.8$; $p = 0.026$) word categories. A significant interaction between *word category* × *group* was also found, $F(5.0,140.9) = 2.49$, $p = 0.034$, $\eta^2 = 0.08$. To rule out that this interaction results from differences in tonic startle reactivity between the groups, an additional rmANCOVA controlling for baseline arousal was calculated, revealing no significant interaction of *baseline arousal* × *group*, $F(2.5,137.9) = 0.55$, $p = 0.616$, $\eta^2 = 0.01$. As indicated in Table 2, the control group showed generally higher EMG startle magnitude than did the patient subsample. Hence, to control for these inter-individual differences, further analysis of startle responses was performed using standardized magnitudes.

3.3. Startle modulation

Fig. 1 presents the startle response modulation relative to the neutral word category. Pairwise group comparisons revealed that the high-FoPA group showed significantly higher startle responses in the negative word category compared to those of the low-FoPA group ($p = 0.014$), and regarding the phobic word category compared to those of both the low-FoPA and healthy group (both $p = 0.003$). There was no attenuation of startle responses in the positive word category in any of the study groups; and the low-FoPA group showed only weak startle response modulation in all word categories.

Regression analysis involving all study groups showed that higher FoPA scores significantly predicted startle potentiation in the phobic word category ($\beta = 0.34$, $p = 0.008$; see Fig. 2), whereas they did not significantly predict EMG magnitudes in the negative ($\beta = 0.23$, $p = 0.075$) word category. The FActS score remained the only significant predictor of startle modulation by phobic words ($\beta = 0.32$, $p = 0.014$) even when controlling for BMI ($\beta = 0.15$, $p = 0.239$) and age ($\beta = -0.11$, $p = 0.379$). Additionally, regression analysis was run exclusively for the patient subsample controlling for LVEF ($\beta = 0.04$, $p = 0.800$), trait anxiety ($\beta = 0.16$, $p = 0.482$), and trait depression ($\beta = -0.30$, $p = 0.178$), resulting in a significant total model, $F(4,37) = 2.76$, $p = 0.044$, $r = 0.50$, with FoPA as significant predictor of startle modulation by phobic priming ($\beta = 0.55$, $p = 0.011$). Hence, FoPA accounted for 30% of the variance in startle potentiation after exposure to phobic words in patients with heart failure when controlling for LVEF, anxiety, and depression; in contrast, FoPA was no significant predictor of startle modulation by negative priming ($\beta = 0.37$, $p = 0.099$), suggesting a specific fear response to physical activity imagery in patients with high FoPA.

3.4. Heart rate response

Table 2 presents mean maximum ΔHR acceleration by prime condition. No main effect of *word category* was observed, $F(2.5,139.1) = 0.63$, $p = 0.569$, $\eta^2 = 0.01$, but a significant interaction of *word category* × *group* emerged, $F(5.0,139.1) = 3.00$, $p = 0.014$, $\eta^2 = 0.10$. This interaction was due to significantly higher HR acceleration in the high-FoPA group in the phobic prime condition ($p = 0.007$) compared to that in the healthy group. Furthermore, the healthy group responded with lower HR acceleration in the positive word category than did the high-FoPA ($p = 0.002$) and low-FoPA group ($p = 0.016$). Group differences in BMI are unlikely to have contributed to the different HR responses of the low-FoPA and the healthy control group in the phobic word condition, as indicated by a repeated rmANCOVA using the term *BMI* × *word category*, which was not significant, $F(2.5,136.3) = 0.82$, $p = 0.467$.

4. Discussion

The overall objective of the present study was to investigate the

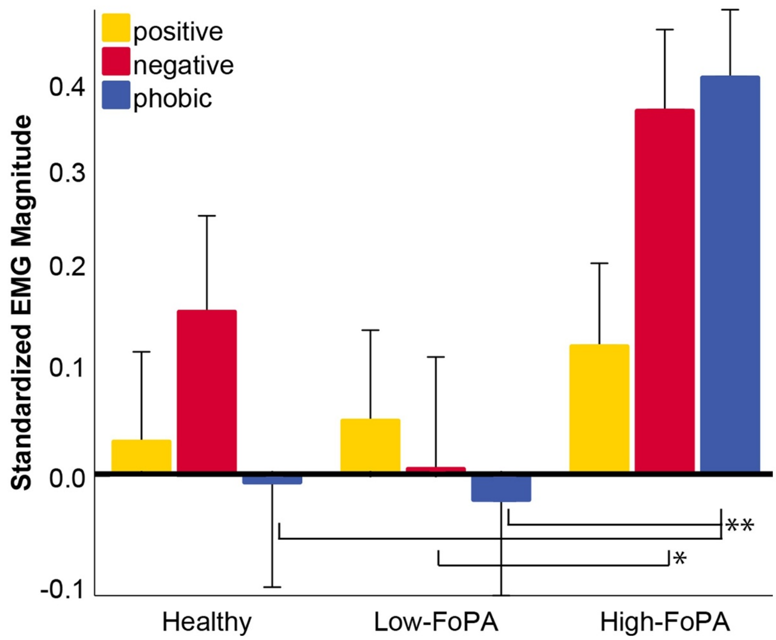

Fig. 1. EMG startle magnitude in the positive, negative, and physical activity-related word category (relative to neutral) of the healthy control group and the patient groups with heart failure scoring either low or high on fear of physical activity (FoPA). Group comparisons indicated by * $p < 0.05$, ** $p < 0.01$. Bars are SEM.

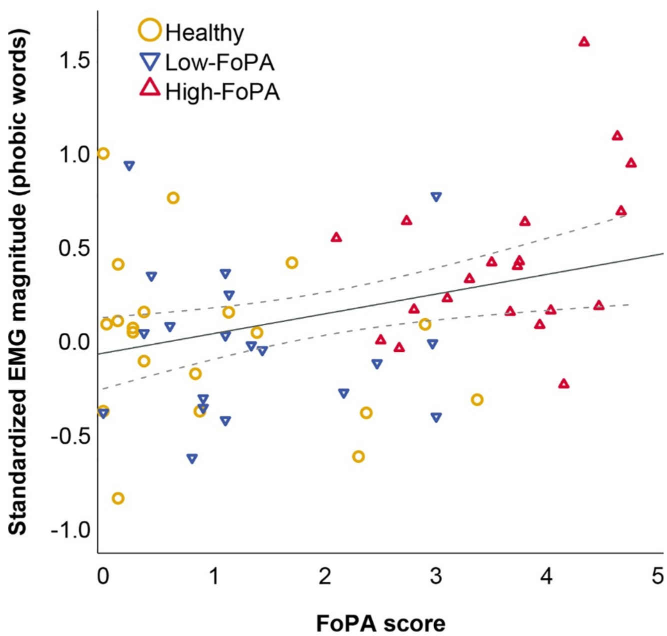

Fig. 2. Scatterplot showing standardized startle responses of healthy adults and patients with heart failure scoring either low or high (sex-specific median split) on fear of physical activity (FoPA; 0 = low; 5 = high) in the physical activity-related word category. Dotted lines around regression line are SEM.

underlying physiological mechanisms of FoPA as measured by the FActS scale in patients with heart failure and in healthy adults. We employed the affective modulation paradigm to assess affective startle and HR response modulation after presenting prototypical lexical stimuli of positive, neutral, and negative valence, as well as words related to physical activity as potentially phobic cues for individuals with high FoPA. First, we examined whether the word categories induced distinct emotional responses in terms of both valence ratings and startle modulation. Second, we investigated whether the exposure to physical activity-related words led to startle potentiation in individuals with high FoPA, and whether this association was independent of general anxiety. Third, we compared HR acceleration responses to emotional words between patients and healthy adults, as an indicator of physiological arousal.

The a-priori assignment of the lexical stimuli to the valence categories based on the BAWL-R normative data was confirmed by participants' valence ratings (from positive over neutral to negative) [33]. Regarding words related to physical activity, both patient groups indicated significantly lower subjective valence compared to the healthy control group, which is in line with reports about a general negative attitude towards physical activity in patients with heart failure [4]. Nonetheless, the valence manipulation worked to induce distinct emotional responses, as indicated by participants' ratings of the stimulus materials, which were also highly correlated with normative data. Although arousal values had been matched across word categories based on normative data, arousal ratings obtained in the present sample differed significantly between the word categories with positive stimuli being most arousing and neutral stimuli being least arousing. However, there were neither significant differences in self-reported arousal between the three study groups, nor differences in baseline EMG that would account for potential tonic differences between groups or word categories.

To our knowledge, the present study is the first to investigate affective startle and HR response modulation by lexical stimuli in cardiac patients. On the one hand, the use of words instead of pictures or animations as priming material allowed a high degree of experimental standardization and internal validity. On the other hand, the use of animations presenting physical activity might induce even greater effects in physiological responses compared to static priming material [12]. We decided, however, to rely on lexical stimuli, as the analysis of HR responses necessitates the precise timing of affective processes evoked by the stimulus, which may be difficult to standardize when using animated stimuli. Nevertheless, our results provide considerable effect sizes of affective modulation by lexical stimuli, which is also supported by other experiments using this kind of stimulus material [11,14,30]. Hence, our findings support the feasibility of the affective modulation paradigm using lexical stimuli to induce affective arousal particularly in cardiac patients.

As expected in the light of both the use of imagery as stimulus material and the positivity bias in older adults who preferably direct their attention to positive stimuli [16,18], our findings revealed no attenuation of startle responses in the positive word category in all three study groups. We would argue that deeper internal information processing of these stimuli is interrupted by sudden air puffs resulting in a defensive response as opposed to rather shallow processing of pictures, which involves mostly external sensory orientation [16,17,37].

The high-FoPA patients showed potentiated startle responses to positive, negative, and phobic words, suggesting a generalized preparedness to mobilize defensive responses in arousing situations. Conversely, the low-FoPA group showed generally weak startle response modulation, in particular after the exposure to negative words, which was a unique characteristic of this group among the other study groups. We assume that these startle modulation patterns of high vs. low FoPA might underlie the emotion-focused coping strategies of avoidance vs. disavowal, respectively, that have been observed in patients with heart failure [6]: Avoidance behavior is associated with general anxiety and is a strategy to reduce affective arousal in unfavorable situations, such as the burden of heart failure symptoms during physical activity. This is corroborated by the findings that patients with high FoPA showed higher anxiety and startle reflex facilitation compared to those in patients with low FoPA, suggesting an activation of the defensive motivational system to prepare avoidance behavior. In contrast, the weak startle response modulation by highly arousing imagery in patients scoring low on FoPA suggests the disavowal of emotional strain as coping mechanism in these patients. Further support for the assumption of different emotion regulation strategies is outlined in another study reporting enhanced vs. suppressed startle modulation, when participants emphatized in imagery vs. distanced themselves from imagery, respectively [38]. Hence, if patients with low FoPA show suppressed startle responses even to negatively valenced imagery, whereas the other two study groups show enhanced responses in this condition, cognitive distancing might dissociate the perception of emotional foreground stimuli (such as disease, breathlessness, and nausea; see Appendix) from its personal impact in patients scoring low on FoPA [6].

Expectedly, the high-FoPA group showed the largest potentiation of startle responses in the phobic word category, whereas the low-FoPA and healthy group showed significantly lower startle responses to physical activity-related words. The physical activity related word category was moderately arousing, as indicated by both normative and study data, which is in line with moderate arousal ratings for sports stimuli reported by Bradley and Sabatinelli [15]. Hence, we assume that these words do not intrinsically evoke high autonomic preparedness because they describe physical activities, but that they elicit emotional responses because of their phobic valence in individuals scoring high on FoPA. The group differences in startle response indicate that words associated with physical activity did not only exert higher self-reported affective responses in patients with high FoPA, but also higher physiological arousal, which may be related to affective processes. These startle modulation patterns were accompanied by pronounced HR acceleration in the phobic and positive conditions, which was significantly higher in the high-FoPA patient group compared to that in the healthy control group, and which are associated with active engagement in memory processing of imagery [16]. Taken together, these findings provide preliminary evidence for sympathetic activation in high-FoPA patients when exposed to phobic stimuli, reflecting the approach-avoidance-system mediated by subcortical-limbic brain structures.

Furthermore, higher FActS scores predicted startle response potentiation after the confrontation with physical activity-related words, independent of the BMI, in the entire sample, indicating that FoPA might also affect certain individuals that are cardiovascularly healthy. On average, healthy controls had a normal BMI, whereas patients tended to be overweight or even obese suggesting that a lack of everyday physical activity might contribute to this. Expectedly, self-reported FoPA was higher in the high-FoPA group compared to that in the low-FoPA and healthy group, while certain individuals in the latter group also reported high FoPA scores. FoPA accounted for 30% of the variance in startle potentiation after phobic priming in the patient subsample, whereas heart failure severity, depression, and anxiety were unrelated to this outcome measure. This finding indicates that startle modulation by verbal cues related to physical activity was not because of high general anxiety in high-FoPA patients, and is in line with a previous study reporting that FoPA, but not anxiety, predicts lower everyday physical activity in patients with heart failure [10]. In addition, our finding is supported by empirical evidence that fear toward a threat cue is mediated by the amygdala, while diffuse anxiety responses are processed in a distinct neural system that does not mediate fear-potentiated startle responses [23]. Considered together, these findings suggest that heart failure patients scoring high on FoPA might avoid physical activity, along with an activated fear network in the brain that mobilizes defensive responses.

In summary, there is multiple evidence for the construct validity of FoPA with regard to cognition (i.e., self-reported worries indicating FoPA), behavior (i.e., lower levels of physical activity), and physiology (i.e., startle potentiation and HR acceleration after exposure to physical activity-related words) [8]. The investigation of physiological arousal mechanisms underlying FoPA suggest that high FoPA is accompanied by enhanced arousal reactivity, which seems to be maladaptive in terms of exercise adherence, whereas low FoPA might be associated with cognitive distancing from the burden of heart failure, which allows engaging in physical activity, and therefore might be a useful coping strategy that could be addressed in interventions to foster physical activity.

5. Conclusions

The present study is the first to assess startle and HR response modulation by emotional words in cardiac patients. Patients with high FoPA responded with startle potentiation and pronounced HR acceleration, indicative of fear processing, when they were exposed to text-driven imagery related to physical activity. Our results support the hypothesis that high FoPA, but not general anxiety and depression, predict startle potentiation and HR acceleration after the exposure to phobic words in patients with heart failure. These findings suggest that exercise regimen might elicit a specific, highly arousing fear (i.e., FoPA) in these patients that activates avoidance behavior at a largely automatic level. Thereby, FoPA might contribute to low adherence to exercise regimen, and should be considered in the clinical management of cardiac patients. Clinical interventions fostering physical activity could address emotion regulation strategies to cope with heart failure.

Ethics and dissemination

Ethics approval was obtained from the ethics committee of the Medical Association of Rhineland-Palatinate / Germany (registration number: 837.465.16 / 10784).

Declaration of Competing Interest

None.

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Appendix: Materials

Neutral words

AUFFORDERN	order
BANNER	banner
ERBETEN	ask for
FUCHS	fox
GEHÖREN	belong
INHALT	content
JUSTIZ	justice
LUPE	magnifying glass
MASKE	mask
MELDEN	report
MERKMAL	feature
PROBE	probe
TATSACHE	fact
TONFALL	sound
VERFÜGEN	dispose
VERLANGEN	request
VERMIETEN	rent
VERMUTEN	assume
WÄHLEN	choose
WUNDERN	wonder

Positive words

BELOHNEN	reward
CHARME	charm
FANTASIE	fantasy
FREUEN	happy
FÜHLEN	feel
GENIEßEN	enjoy
GEWINN	win
GLÜCK	luck
HEILUNG	healing
KLUGHEIT	wisdom
LÄCHELN	smile
LEUCHTEN	gleam
LOBEN	praise
MUT	courage
SCHENKEN	donate
SEHEN	see
SOMMER	summer
STRAHLEN	shine
TOLERANZ	tolerance
VERTRAUEN	trust

Physical activity-related words

AKTIVITÄT	activity
AUSDAUER	endurance
BALL	ball
BEWEGUNG	motion
FAHRRAD	bike
GEHEN	walk
HEBEN	lift
LAUFEN	run
RENNEN	sprint
RUDER	paddle
SEX	sex
SPORT	sport
SPRUNG	jump
STEIGEN	climb
TANZEN	dance
TAUCHEN	dive
TRAGEN	carry

TREPPE	stairs
WANDERN	hiking
WERFEN	throw

Negative words

AAS	carrion
ABFALL	waste
ANGEBEN	show off
ATEMNOT	breathlessness
AUFGEBEN	give up
BEAMTE	official
BEFÜRCHTEN	fear
FEHLEN	missing
KOSTEN	cost
KRANKHEIT	disease
MAKEL	defect
MIETE	rent
MÜSSEN	must
STÜRZEN	fall
TABLETTE	pill
TRAUERN	sorrow
ÜBELKEIT	nausea
UNLUST	unpleasure
VERLETZEN	injury
VERLIEREN	loose

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