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ORIGINAL ARTICLE

Psychophysiological Reactivity, Interoception and Emotion Regulation in Patients with Agoraphobia During Virtual Reality Anxiety Induction

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Abstract The symptoms experienced by patients with agoraphobia are often attributed to excessive autonomic arousal, but recent theories postulate blunted rather than enhanced autonomic reactivity. Cognitive models explain this contrast by distorted interoception, possibly linked to dysfunctional emotion regulation under stress. In the current study, physiological measures were compared directly to their subjective perception in patients with agoraphobia ($n = 21$) and healthy controls ($n = 27$) in a virtual reality stressor. Blunted reactivity was confirmed for heart rate and parasympathetic influences on heart rate variability, but measures of sympathetic activation did not differ between groups. As expected, patients showed exaggerated perception of their physiological response. Usage of emotion regulation strategies during the stressor did not differ between groups, but patients reported strong difficulties in perception of and coping with emotions in a trait measure. Our findings suggest that distorted perception of physiological and emotional processes is central to agoraphobia.

Keywords Agoraphobia · Psychophysiology · Interoception · Emotion regulation · Virtual reality · Bodily sensations · Panic disorder

Introduction

Patients with agoraphobia fear being overwhelmed by panic attacks or other intense physical sensations. They thus avoid situations likely to induce such symptoms without the possibility of flight or prospect of help (American Psychiatric Association 2013), or rely on rigid and dysfunctional coping strategies ("safety behaviors"). While symptoms of physiological hyper-reactivity feature prominently in patient reports, research on that topic is contradictory. There are reports of increased sympathetic nervous system (SNS) activity (Roth et al. 1986) and reactivity (Stein et al. 1992) in patients with panic disorder with our without agoraphobia (PDA),[1] but these findings have later been cast into doubt by more rigorous studies (Stein and Asmundson 1994), leaving the SNS's role in panic disorder unresolved (for an overview see Friedman and Thayer 1998). Lang and McTeague (2009) recently introduced the hypothesis of an anxiety disorder spectrum, which predicts increased psychophysiological reactivity for disorders characterized by episodic fear (such as specific phobias) and reduced reactivity for disorders characterized by chronic anxiety, most prominently panic disorder *with* agoraphobia. This concept has so far only been investigated in memory cue/imagery studies (e.g. Cuthbert et al. 2003). Thus, it remains unclear whether the lack of reactivity in patients with agoraphobia is due to peculiarities of memory organization, anomalies in autonomic nervous system

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[1] Our study focus is agoraphobia, with special emphasis on the chronicity of anxiety that is not shared with panic disorder alone. Even though DSM-5 introduced agoraphobia as an independent diagnostic category, much relevant research has been conducted using the DSM-IV diagnosis of panic disorder with (or without) agoraphobia. We present such research where it is relevant to our study, using the authors' original diagnostic terms (i.e. panic disorder).

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functioning, or other factors. Furthermore, if objective physiological responses are reduced, pathways to contradictory subjective experiences need to be detailed. Our study searches to elaborate on these questions.

As Lang and McTeague (2009) emphasized chronic negative affectivity as a cause of reduced reactivity, emotion regulation (ER; Gross 1998) plausibly contributes to these anomalies. Extensive research has linked high levels of dysfunctional ER strategies to anxiety disorders (Aldao et al. 2010; Amstadter 2008). Hofmann and colleagues (Hofmann et al. 2012) recently summarized research on ER and concluded that dysfunctional ER strategies are at the core of mood and anxiety disorders. Dysfunctional ER strategies like suppression are reported to intensify subjective experience of negative emotions (Campbell-Sills et al. 2006b), especially in the presence of high habitual emotional avoidance (Feldner et al. 2003). Importantly, negative affect has been demonstrated to linger on after trying to suppress emotions (Campbell-Sills et al. 2006a), illustrating how suppression efforts might contribute to chronic negative affectivity. Reappraisal, on the other hand, is considered an adaptive ER strategy, which allows using emotional information for problem-solving (Hofmann et al. 2012). Psychophysiological reactivity has been found to paradoxically increase in participants instructed to suppress their emotions (Campbell-Sills et al. 2006b). When suppression is used habitually and spontaneously, on the other hand, physiological responses appear dampened (Sloan 2004). Thus, participant's habitual as well as momentary use of ER strategies will be of interest to our study.

For flexible emotional responding, parasympathetic nervous system (PNS) activity is supposed to be central (Appelhans and Luecken 2006; Porges et al. 1994), and is frequently measured through the spectral power of high-frequency heart rate variability (HF-HRV) (Friedman and Thayer 1998). Reduced HF-HRV in PDA is generally supported by the literature (Cohen et al. 2000; Klein et al. 1995; Pittig et al. 2013), with few exceptions (Slaap et al. 2004). Thus, anxiety disorders seem to be characterized by a reduced range of physiological as well as behavioral responses (Friedman 2007). While reduced HF-HRV is supposed to imply reduced reactivity, direct studies of PNS response to stressors in PDA are scarce, with some studies reporting no differences to healthy controls (Blechert et al. 2007; Wang et al. 2013) and others supporting reduced reactivity in PDA (Cohen et al. 2000). Thus, more research on differential response of SNS and PNS branches in PDA is needed.

The gap between actual and perceived bodily reactions has been addressed by cognitive theories (Clark 1986; Hoehn-Saric and McLeod 2000). There is ample evidence for the theorized misinterpretation of bodily sensations from different questionnaire studies (see Austin and Richards 2001, for an overview) and for increased interoceptive sensitivity (i.e. accuracy in heart beat perception, Domschke et al. 2010) as well as body vigilance (Schmidt et al. 1997). These processes also contribute to ER anomalies (Tull et al. 2008) insofar as emotional states in general are feared and avoided because of the accompanying bodily response. However, perception of bodily sensations has never been compared with measurements of these symptoms during stress.

The aim of the present study was to assess psychophysiological, interoceptive and emotion regulation variables in response to a virtual reality (VR) stressor, comparing panic patients with pronounced agoraphobic avoidance (PA) with a healthy control group (HC). Our stressor scenario simulates an emergency situation without immediate threat to survival, and takes place in an underground parking garage, thus inducing fear independently of disorder while also incorporating some agoraphobic aspects. In accordance with the theories and findings presented above, we hypothesized: (1) reduced sympathetic and parasympathetic reactivity but (2) increased perception of bodily sensations in PA group and (3) greater general difficulties in ER as well as more use of dysfunctional (suppression) than functional (reappraisal) ER strategies in PA group.

Methods

Participants

The initial sample consisted of 23 patients with panic disorder and/or agoraphobia (PA) and 28 healthy controls (HC). One patient could not finish the experiment due to intense nausea in the virtual reality, and data of one participant in PA and HC group, each, were lost due to technical problems, leaving a final sample of $n = 21$ (PA) and $n = 27$ (HC). Patients were recruited after self-presenting to the outpatient clinic of the Department of Psychology as well as through newspaper articles. Patients participated voluntarily without financial compensation and received diagnostic assessments and treatment in a specialized psychotherapeutic protocol for agoraphobia independently of study participation. Healthy controls were recruited through department bulletin notices. They were rewarded through course credit and possibility to win vouchers in a lottery. The study design was approved by the institutional ethics committee.

After giving informed consent, all participants underwent a structured clinical interview (SKID; Wittchen et al. 1997; German version adapted from SCID-I: First et al. 1996), including SKID-II for personality disorders in the

patient group. Participants in the patient group met a current diagnosis of panic disorder with ($n = 18/86$ %) or without agoraphobia ($n = 1/5$ %) or agoraphobia without panic disorder ($n = 2/10$ %) according to DSM-IV (APA 2000). Reported duration of the disorder averaged 14.34 years (SD = 11.06; range 0.75–39). Patients reported an average of 8.45 panic attacks in the last four weeks (SD = 26.35). Comorbidities were allowed (and are present in $n = 2/10$ % of patients; one participant with Dysthymia and Generalized Anxiety Disorder, one with an eating disorder NOS), but current psychosis, bipolar disorder, borderline personality disorder, substance dependence and medication with benzodiazepines were exclusion criteria, as they were considered detrimental to the psychotherapeutic treatment program that participants were eligible for. No potential participant met any of these criteria. Only three patients (14 %) received psychotropic medication, all with SSRI class antidepressants. Participants in the healthy control group did not meet the criteria for any current DSM-IV diagnosis. All participants had to be between 18 and 65 years of age.

Gender did not differ significantly between groups, with a slight majority of female participants in both PA (n = 15/71 %) and HC (17/63 %) groups. As can be seen in Table 1, participants in PA group were older on average than participants in HC group. They did not differ, however, in their gaming proficiency, as measured by responses to a single item "how good are you at playing computer games?", rated on a 5-point scale from 0 ("no experience") to 4 ("very good"). As expected, PA participants scored significantly higher in general psychopathology measured by the Brief Symptom Inventory General Severity Index (BSI-GSI; Derogatis and Spencer 1982; german version Franke 1997). The same was true of depressive symptoms assessed with the Beck Depression Inventory II (BDI-II; Beck et al. 1996; german version Hautzinger et al. 2006), with PA average scores falling in the range of 14–19 points indicating mild depressive symptoms. Panic and agoraphobia symptom scores were assessed using the Agoraphobic Cognitions Questionnaire and Body Sensation Questionnaire (Chambless et al. 1984) as well as the Mobility Inventory for Agoraphobia "alone" scale (Chambless et al. 1985). Patients in our sample scored significantly higher than the healthy control group with average scores at or slightly below the German reference sample scores (Ehlers and Margraf 2001). Healthy control group scores were at or below reference values for all symptom scales.

Table 1 Sample characteristics in panic/agoraphobia (PA) and healthy control (HC) groups

	PA [*M* (*SD*)]	HC [*M* (*SD*)]	*d*
Age (years)	43.43 (12.08)	22.70 (4.44)	2.40***
Gaming proficiency	1.53 (1.43)	2.19 (1.27)	0.50
BSI	0.83 (0.47)	0.20 (0.18)	1.90***
BDI-II	14.26 (6.56)	3.26 (2.96)	2.30***
ACQ	1.97 (0.68)	1.38 (0.22)	1.28**
BSQ	2.69 (0.67)	1.81 (0.44)	1.62***
MI-A	2.50 (0.85)	1.24 (0.24)	2.23***

M mean, *SD* standard deviation, *d* Cohen's d effect size of mean difference between groups, *BSI* Brief Symptom Inventory General Severity Index (GSI), *BDI-II* Beck Depression Inventory-II sum score, *ACQ* Agoraphobic Cognitions Questionnaire mean score, *BSQ* Body Sensations Questionnaire mean score, *MI* Mobility Inventory for Agoraphobia mean score

t test for mean difference between groups: * $p < .05$; ** $p < .01$; *** $p < .001$

Procedure

After filling in questionnaires (the diagnostic interview usually took place on a separate day prior to the experiment), participants were seated in a darkened room and set up for psychophysiological recording. The interface for the participant consisted of a computer screen, a joystick, and a head-mounted display equipped with headphones and a tracer for head movements. For technical details of the virtual reality scenarios programming as a 3D first person simulation see Becker-Asano et al. (2011).

The experiment comprised five conditions in constant order: a (1) *baseline* (5 min) assessment while showing a calm video clip of a monk walking in a garden; a (2) *training* (5 min) scenario in the virtual reality environment, in which the relevant controls were introduced and practiced using simple tasks. Standardized instructions were delivered through the headphones and visual indicators within the virtual reality. The training session was framed in a story that also introduced the scenario to be used subsequently: Participants made their way in an underground parking garage from a parked car identified as theirs to the exit using an elevator. The instructions went on to state that they would meet friends outside to watch a movie. In the (3) *experimental scenario* (1–3 min)[2] participants were asked to imagine returning from the movie theater and were instructed to take the elevator down and return to their car in order to pick up their friends waiting outside the parking garage. They were told that something unexpected might happen and to behave as they would in real life. The (4) *stressor scenario* (1–3 min) began once participants passed a certain threshold near their car. This was marked by the sound of an explosion and a screaming

[2] Because time spent in the scenario and stressor conditions varied between participants, one to three minutes were used for psychophysiological analyses in each condition, depending on individual availability. Analyses did not change substantially when only using each participant's first minute in these two conditions.

person as well as dimmed lighting. Moving further, participants saw their own car and an adjacent pickup truck on fire, emanating smoke that was thickening over time. A person was visible near the truck with their legs trapped under fallen goods. To add to the immersion, a smoke perfume was applied subtly to a cloth near the participant at this time. Participants were able to press a fire alarm button at several locations on the walls, pick up and use a fire extinguisher or duck to move under the smoke, but it was impossible to put out the fire or move the trapped person. Harm to the participants themselves was indicated through coughing sounds and red flashes of the HMD screens when moving in the smoke or too near to the flames. The simulation ended when participants left the scenario either through one of the emergency exits or the car exit ramp, or pressed the elevator button. As a (5) *relaxation* baseline, participants were subsequently asked to remain in the dark room and relax for 5 min.

The ratings of anxiety and interoceptive sensations were taken immediately after each condition (with exception of the first part of the experimental scenario, because it was followed by the stressor scenario without leaving the virtual reality). The self-report measure on usage of emotion regulation strategies during the stressor scenario was taken once right after the scenario.

Psychophysiological Measures

Heart rate (HR) and skin conductance level (SCL) were chosen as well-established indicators of fear response (Kreibig et al. 2007), SCL being especially useful as a proxy of SNS activity (Jacobs et al. 1994). Power in the high frequency band of heart rate variability (HF-HRV: 0.14–0.5 Hz) was used as indicator of PNS cardiac influence (Appelhans and Luecken 2006), calculated via complex demodulation, which is especially useful for short time periods and to assess response to stressors (Wilhelm et al. 2005).[3] Data was recorded continually throughout the experiment at 512 Hz using a Varioport-II portable device (Becker-Meditec, Karlsruhe, Germany). The experimenter marked the different experimental conditions by pressing an integrated button. Electrodermal activity was measured by two electrodes placed on the middle phalanges of the third and fourth digit of the non-dominant hand so as to interfere minimally with the virtual reality controls. Electrocardiogram measures were taken from three leads placed on both ends of the sternum and on the lower left costal margin, a lead placement that minimizes interference from muscle activity.

[3] While the ratio of power in the low frequency band to that in the high frequency band was frequently reported as an indicator of cardiac SNS activity, such a connection has been refuted convincingly (Goedhart et al. 2008). Another measure of parasympathetic control of heart rate frequently reported in the literature, the time domain based square root of the mean squared differences of successive NN intervals (RMSSD) yielded results very similar to the HF-HRV we report.

Self-Report Measures

Emotion Regulation Questionnaire (ERQ; Gross and John 2003; German Version Abler and Kessler 2009)

The ERQ is a widely used 10-item measure yielding scales for the emotion regulation strategies reappraisal (6 items, e.g. "I control my emotions by changing the way I think about the situation") and suppression (4 items, e.g. "I control my emotions by not expressing them"). Participants indicate how well each item describes their behavior on a scale from 1 (strongly disagree) to 7 (strongly agree). Reappraisal is considered an antecedent-focused strategy with generally beneficial consequences, whereas suppression is seen as a generally maladaptive response-focused strategy (Gross and John 2003). Reliability of both scales is considered acceptable, with reported Cronbach's alpha of .79 and .73 for the German version's reappraisal and suppression scales, respectively (Abler and Kessler 2009).

Emotion Regulation Questionnaire-State (ERQ-S; Egloff et al. 2006)

To assess usage of the emotion regulation strategies reappraisal and suppression during the stress scenario, we used two brief 3-item scales developed by Egloff et al. (2006) on the basis of the corresponding ERQ scales (Gross and John 2003). Thus, the reappraisal scale consisted of: "I tried to see the situation as positive as possible," "I viewed the situation as a challenge," and "I thought of the situation in a way that made me stay calm." The suppression scale comprised the item "During the situation, I controlled my emotions" and the reverse scored items "I showed my emotions" and "One could see my feelings during the situation." Participants indicated on a 6-point scale ranging from 0 (not at all) to 5 (extremely) which emotion regulation behavior they used immediately after the stressor scenario. Reliability of both scales is reported as acceptable ($\alpha s > .7$; Egloff et al. 2006), but in our sample was acceptable only for the reappraisal scale ($\alpha = .70$) and poor for the suppression scale ($\alpha = .46$).

Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer 2004; German Version Ehring et al. 2008)

The DERS is a 36-item measure emphasizing awareness, understanding, and acceptance of emotions next to the

modulation of emotional arousal. Thus, the six subscales comprise lack of emotional *awareness* (e.g. "I pay attention to how I feel" [reverse scored]), lack of emotional *clarity* ("I am confused about how I feel"), *non-acceptance* of emotions ("When I'm upset, I feel guilty for feeling that way"), limited access to regulation *strategies* ("When I'm upset, it takes me a long time to feel better"), *impulse* control difficulties ("When I'm upset, I feel out of control"), and difficulties engaging in *goal*-directed behavior when distressed ("When I'm upset, I have difficulty concentrating"). Participants indicate how often each item applies to themselves on a 5-point scale ranging from 1 (almost never) to 5 (almost always). Scales are coded such that higher scores indicate greater difficulties in emotion regulation. All scales are reported to have adequate to good internal consistencies ($\alpha s > .8$) both for the original (Gratz and Roemer 2004) and the German versions (Ehring et al. 2008).

State Single-Item Scales of Anxiety and Interoceptive Sensations

To assess subjective distress and perception of bodily reactions, participants indicated on 11-point scales ranging from 0 (not at all) to 10 (very intense) how strongly they had experienced each of the following after each experimental condition: *anxiety* ("How intense was your anxiety during the [film/training/…] when it was most intense?"), *heartbeat perception* ("How intensely did you perceive your heartbeat during the […]?"), and *sweat perception* ("How intensely did you sweat during the […]?").

Data Analysis

All psychophysiological channels were edited manually to remove movement and electronic artifacts as well as ectopic beats in the electrocardiogram (ECG), using ANSLAB software version 2.51 (Wilhelm and Peyk 2007). Data quality was generally very high, resulting in valid data for all subjects in all tasks. Average scores within 1-min intervals were exported and then averaged again for each condition.

Both autonomic nervous system and self-report repeated measures taken during the experiment were modelled as linear mixed effects using the lme4 (Bates et al. 2014, 2015) package for the statistics software R (R Core Team 2014). Participant was included as a random effect. Experimental condition and group as well as their interaction were included as fixed effects and tested for overall statistical significance with Chi square-based likelihood ratio tests. Planned contrasts were used to compare each condition to the film baseline, with the appropriate *t* test approximation from the lmerTest package (Kuznetsova et al. 2015), thus controlling for baseline differences.

Results

Autonomic nervous system and self-report measures taken during the experiment are presented in Table 2 along with results from the HLM modeling. Results for subjective anxiety constitute a manipulation check, with the significant main effect of experimental condition along with the significant contrast for stressor (vs film) showing that the experimental induction worked for both groups. While the group × condition interaction was also statistically significant, the crucial group × stressor interaction contrast was not, marking similar levels of anxiety in the stressor condition between groups.

Our first hypothesis of reduced physiological reactivity is concerned with group by condition interactions in the following. Both groups responded with accelerated heart rate to the scenario and stressor conditions. The significant interaction effect and contrast for stressor indicate that PA group responded with less heart rate increase than HC group to the stressor (see Fig. 1). For skin conductance level, both groups responded equally, indicating increasing sympathetic activation during the stages of the experiment up to the stressor, with no significant interaction. Heart rate variability in the high frequency spectrum (HF-HRV) responded with the expected decline in both groups, indicating parasympathetic withdrawal up to the stressor condition and restitution during relaxation. The significant interaction effect and contrast for stressor indicate that this parasympathetic withdrawal from film to stressor conditions was less pronounced in PA than HC group (see Fig. 2).

For the second hypothesis of increased interoception, the following group by condition interactions are relevant. Perception of one's own heartbeat was significantly increased for both groups in stressor and relaxation conditions, and heartbeat was perceived more strongly by PA group than HC group in training and stressor conditions, as the interaction contrasts indicate (see Fig. 3). Sweat perception was increased in both groups for all conditions from the film baseline, and as the marginally significant interaction indicates more strongly so in PA group than HC group. To directly test the differences between psychophysiological parameters and corresponding self-reported interoception, we modelled values for HR together with heartbeat perception, and SCL together with sweat perception,[4] adding one more factor to the models otherwise as reported above. The group by variable interaction of interest was significant both for HR versus heartbeat perception [$X^2(1) = 10.81$, $p = .001$] and SCL versus

[4] All values were z-standardized, and the ibi values used as HR indicators were inverted so that higher values indicate faster heartbeat in accordance with the self-report measures.

Table 2 Autonomic nervous system and self-report measures descriptive and inferential statistics by experimental condition in panic/agoraphobia (PA) and healthy control (HC) groups

	PA	HC	Group			Experimental condition			Group × condition		
	M (SD)	M (SD)	X^2	*df*	*p*	X^2/t	*df*	*p*	X^2/t	*df*	*p*
Anxiety (0-10)			9.39	1	.002**	106.95	3	<.001***	15.15	3	.002**
Baseline	0.76 (1.34)	0.89 (1.50)									
Training	3.57 (2.64)	1.04 (1.13)				3.99	137.24	<.001***	3.59	137.24	<.001***
Stressor	5.71 (2.95)	5.11 (1.99)				12.37	137.24	<.001***	0.98	137.24	.327
Relaxation	2.95 (2.82)	1.19 (1.44)				3.34	137.61	.001**	2.54	137.61	.012*
HR (ibi ms)			0.01	1	.903	99.04	4	<.001***	14.1	4	.007**
Baseline	834.94 (120.67)	839.09 (98.82)									
Training	807.72 (116.21)	836.03 (116.78)				1.51	184.02	.133	1.2	184.02	.230
Scenario	798.32 (120.16)	793.55 (133.39)				4.1	184.02	<.001***	0.45	184.02	.657
Stressor	777.01 (131.31)	731.75 (127.96)				8.24	184.02	<.001***	2.46	184.02	.015*
Relaxation	856.77 (119.91)	855.10 (103.00)				1.89	184.02	.061	0.29	184.02	.772
SCL (μS)			0.09	1	.769	122.72	4	<.001***	1.47	4	.833
Baseline	2.57 (1.71)	2.44 (1.52)									
Training	3.11 (1.78)	2.98 (1.56)				7.53	184	<.001***	0.01	184	.989
Scenario	3.24 (1.65)	3.13 (1.48)				9.44	184	<.001***	0.14	184	.886
Stressor	3.40 (1.63)	3.34 (1.52)				11.92	184	<.001***	0.48	184	.634
Relaxation	3.25 (1.62)	3.03 (1.33)				8.81	184	<.001***	0.68	184	.499
HF-HRV (log power)			6.34	1	.012*	57.02	4	<.001***	14.01	4	.007**
Baseline	6.84 (0.93)	7.59 (1.03)									
Training	6.28 (1.04)	7.26 (0.94)				3.48	184	<.001***	0.91	184	.364
Scenario	6.42 (0.93)	6.98 (1.12)				4	184	<.001***	0.75	184	.457
Stressor	6.32 (1.12)	6.42 (1.04)				6.56	184	<.001***	2.54	184	.012*
Relaxation	6.79 (1.08)	7.61 (1.04)				0.13	184	.895	0.24	184	.811
Heartbeat perception (0–10)			9.4	1	.002**	50.84	3	<.001***	11.26	3	.010*
Baseline	1.71 (2.17)	1.70 (2.20)									
Training	3.24 (2.17)	0.78 (1.05)				0.79	137.21	.430	3.24	137.21	.001**
Stressor	5.19 (2.38)	3.48 (2.24)				6.95	137.21	<.001***	2.25	137.21	.026*
Relaxation	4.00 (2.70)	2.88 (2.12)				4.56	137.53	<.001***	1.46	137.53	.146
Sweat perception (0–10)			6.17	1	.013*	61.85	3	<.001***	6.65	3	.084
Baseline	0.62 (0.80)	0.56 (1.12)									
Training	2.38 (2.46)	0.93 (1.30)				3.19	137.15	.002**	2.08	137.15	.040*
Stressor	4.24 (3.33)	2.85 (2.21)				8.84	137.15	<.001***	1.98	137.15	.050
Relaxation	2.62 (2.99)	1.08 (1.32)				3.77	137.39	<.001***	2.18	137.39	.031*

M mean, *SD* standard deviation, X^2 omnibus HLM test statistic in rows with measure names, *t* *t* test of planned contrast for each condition with film baseline as reference, *df* degrees of freedom, *p* *p* value. *HR* heart rate (calculations were performed on inter beat interval [*ibi*] measured in ms), *SCL* skin conductance level, *HF-HRV* high frequency band power of heart rate variability (0.14–0.5 Hz, log of power)

* $p < .05$; ** $p < .01$; *** $p < .001$

sweat perception [$X^2(1) = 6.33$, $p = .012$], indicating a more pronounced interoception in PA group. Three way interactions (group by condition by variable) were not significant for SCL vs sweat perception [$X^2(3) = 2.96$, $p = .397$] and only marginally significant for HR vs heartbeat perception [$X^2(3) = 6.13$, $p = .105$]. Thus,

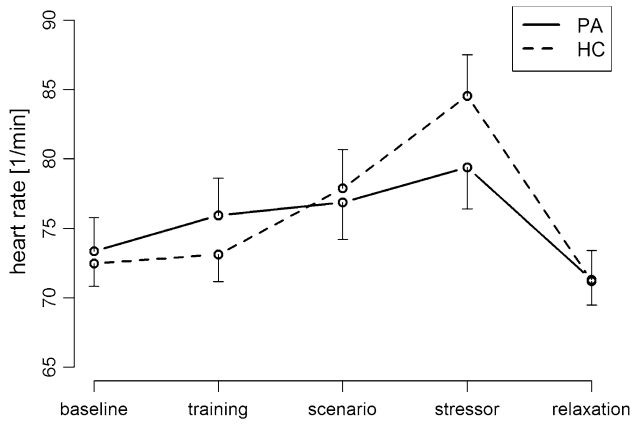

Fig. 1 Mean levels of heart rate in panic/agoraphobia (*PA*) and healthy control (*HC*) groups by experimental condition (inter beat interval was used for all calculations, but heart rate is plotted to facilitate interpretation)

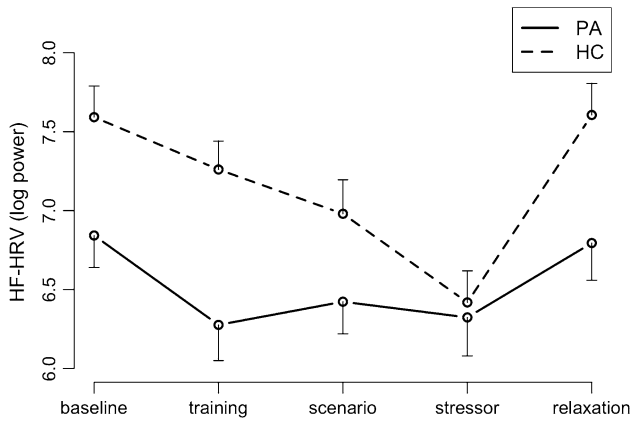

Fig. 2 Mean levels of high frequency band power of heart rate variability (HF-HRV; 0.14–0.5 Hz; indicative of parasympathetic activation) in panic/agoraphobia (*PA*) and healthy control (*HC*) groups by experimental condition

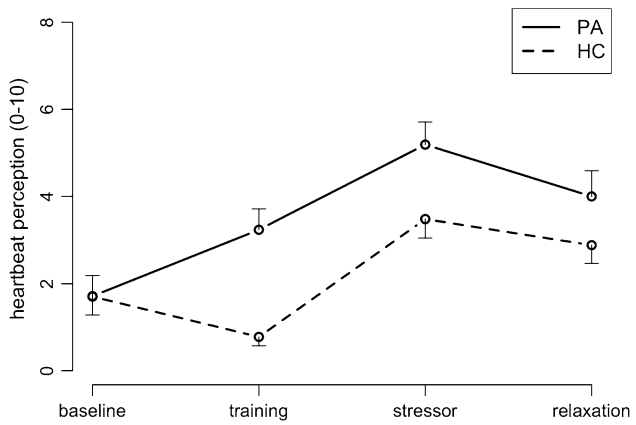

Fig. 3 Mean levels of self-reported heartbeat perception in panic/agoraphobia (*PA*) and healthy control (*HC*) groups by experimental condition

discrepancies between psychophysiological parameters and corresponding self-reported interoception did not depend strongly on the experimental condition, even though interaction contrasts for HR versus heartbeat perception indicate they were slightly more pronounced in the stressor [vs baseline, $t(320.97) = 2.33$, $p = .021$] and training [$t(320.97) = 1.69$, $p = .092$] conditions (compare also Figs. 1 and 3).

To test our third hypothesis, usage of emotion regulation strategies (Fig. 4) was analyzed in a hierarchical linear model with fixed effects *strategy* (suppression vs reappraisal), *state-trait* (ERQ-S vs ERQ scores) and *group* (PA vs HC), including subject as a random effect. As expected, there was no overall group effect [$X^2(1) = 0.14$, $p = .709$]. The main effect of strategy [$X^2(1) = 6.46$, $p = .011$] indicates higher overall usage of reappraisal ($M = 3.26$, $SD = 1.79$) compared to suppression (2.81, 1.11), but has to be regarded cautiously because of interaction effects. A significant state-trait by strategy two-way interaction [$X^2(1) = 32.93$, $p < .001$] indicates that both groups reported to use more reappraisal than suppression in the trait questionnaire, but more suppression than reappraisal for the state measure. The significant three-way interaction [$X^2(1) = 3.89$, $p = .049$] can best be interpreted as trait usage of reappraisal being even more pronounced in HC compared to PA group (see Fig. 4). The other two-way interactions were not statistically significant ($ps > .1$).

Further testing our third hypothesis, difficulties in emotion regulation (DERS) were analyzed with *t* tests for each scale. As displayed in Table 3, PA participants reported significantly more difficulties in emotion regulation across all different aspects with large effect sizes.

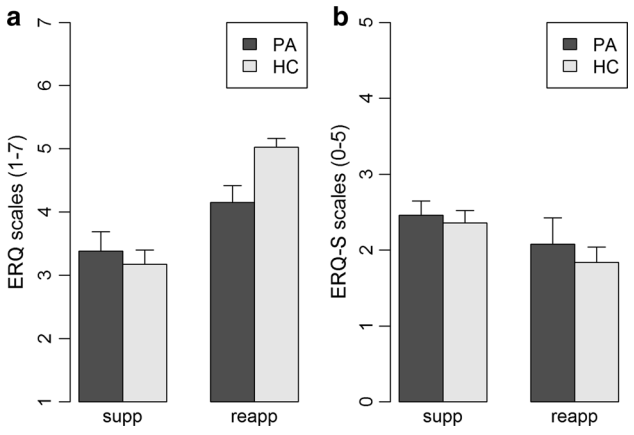

Fig. 4 Mean levels of **a** trait (*ERQ* Emotion Regulation Questionnaire) and **b** state (*ERQ-S* Emotion Regulation Questionnaire-State) emotion regulation with strategies suppression (*supp*) and reappraisal (*reapp*) in panic/agoraphobia (*PA*) and healthy control (*HC*) groups

Table 3 Difficulties in emotion regulation (DERS subscales) in panic/agoraphobia (PA) and healthy control (HC) groups

	PA *M* (*SD*)	HC *M* (*SD*)	*t*	*df*	*p*	*d*
Awareness	2.61 (0.82)	1.80 (0.67)	3.56	33.90	.001**	1.10
Clarity	3.05 (0.70)	2.30 (0.95)	3.05	43.83	.004**	0.87
Non-acceptance	2.32 (0.83)	1.51 (0.48)	3.81	26.50	<.001***	1.25
Strategies	3.14 (0.93)	2.31 (0.68)	3.28	30.99	.003**	1.04
Impulse	2.76 (0.82)	1.67 (0.69)	4.73	34.46	<.001***	1.46
Goal	2.47 (0.51)	1.80 (0.55)	4.27	40.80	<.001***	1.26

M mean, *SD* standard deviation, *t* test for mean difference between groups *t* value *t* and degrees of freedom (*df*), *d* Cohen's d effect size of mean difference between groups

* $p < .05$; ** $p < .01$; *** $p < .001$

Discussion

It has recently been suggested that chronic anxiety disorders like agoraphobia show not enhanced, but rather blunted psychophysiological reactivity (Lang and McTeague 2009). The contrasting patient self-reports can be explained by cognitive models emphasizing distorted interoception (Clark 1986) in the context of dysfunctional emotion regulation (ER) when confronted with external stressors and intense emotional states (Amstadter 2008; Barlow 2002). While the psychophysiological, cognitive and ER levels of observation are conceptually linked, they had never, to our knowledge, been studied together. Our study addressed this shortcoming in the literature using an innovative virtual reality stressor that forced participants to respond to an anxiety-inducing scenario, thus increasing ecological validity.

As hypothesized, decreased reactivity in the panic/agoraphobia (PA) group compared to healthy control (HC) group could be shown for heart rate (HR) and parasympathetic influences on the heart (HF-HRV). This extends findings from Lang and colleagues (Cuthbert et al. 2003; Lang and McTeague 2009; McTeague et al. 2011), who have shown decreased reactivity in chronic anxiety disorders in several imagery studies with eye-blink startle potentiation as the main outcome. Using an external stressor rather than imagery cues, our findings are also suggestive of causes for this dampened reactivity. Lang and McTeague (2009) emphasize less coherent memory networks in chronic anxiety disorders. Our replication with an external stressor, which should rely less on memory activation, suggests general dysfunctions in the autonomic nervous system.

Contrary to our hypothesis, SCL as a measure of sympathetic activity showed no group difference in response to the stressor. This is in line with other carefully controlled findings of no difference in sympathetic functioning between patients with panic disorder and healthy controls in response to a range of physiological stressors (Stein and Asmundson 1994) and supports theoretical claims that self-reported autonomic symptoms cannot simply be mapped on sympathetic aberrations in panic disorder (Friedman 2007). In line with arguments against a simple autonomic continuum from sympathetic to parasympathetic dominance (Berntson et al. 1991), our differential findings for sympathetic and parasympathetic reactivity also suggests that these branches need to be modelled separately in theories of autonomic functioning in anxiety disorders. Beauchaine (2001) has built on work from Gray (1987) and Fowles (1980) in combination with Porges' (2007) polyvagal theory and proposed a framework for autonomic functioning in psychopathology that differentiates parasympathetic and sympathetic pathways. In this view, the parasympathetic branch provides unspecific fight/flight reactivity, while the sympathetic branch expresses the specific motivational states of behavioral activation or inhibition. Put into this context, our findings would suggest that patients with agoraphobia are less able to launch the fight/flight reaction in the face of external stressors but are unimpaired in the specifics of their motivational response. The observed deficits in parasympathetic *reactivity* align well with the tonically reduced parasympathetic *activity* reported in the literature (Friedman 2007), which is also apparent in our sample as differences at baseline and across tasks other than the stressor (compare Fig. 2). On a psychological level, low HF-HRV is connected to self-regulatory processes (Reynard et al. 2011). The lowered HF-HRV in patients with PDA could thus be an indicator of either low self-regulatory strength as a trait, or alternatively of chronically exhausted self-regulatory capacity (i.e. "fatigue"; Segerstrom and Solberg Nes 2007), possibly due to constant attempts at regulating sensations of anxiety. If future research confirms and clarifies this connection, we could learn whether strengthening self-regulation, or learning to apply it more selectively (or both), are viable targets for psychotherapy.

In contrast with the psychophysiological findings, subjective perceptions of heartbeat and sweat were increased in PA compared to HC group, in line with our hypothesis of distorted interoception. This discrepancy was also

confirmed in a direct statistical test of interaction between corresponding psychophysiological and self-report measures. Extending research on cardiac interoceptive sensitivity (Domschke et al. 2010), our finding directly supports the notion of exaggerated interoception, which had so far mostly been induced from better heartbeat detection in anxious patients (e.g. using the paradigm of Schandry 1981), and shows that similar processes are active for sweat as well as heartbeat. The possible contribution of increased perception of nonspecific skin conductance fluctuations to distorted appraisal of arousal has recently been shown for GAD (Andor et al. 2008), and would now be interesting to replicate in PDA. Together with existing literature on panic patients' tendency to expect harm from bodily sensations (Austin and Richards 2001), our finding thus supports cognitive (Clark 1986) and psychophysiological (Ehlers et al. 1988) models of panic disorder.

In contrast to our hypothesis, ER strategy usage did not differ strongly between groups, with statistically significant indication only of less habitual reappraisal in PA compared to HC group, but no differences concerning ER during stress. Supporting our hypothesis, however, we found strong evidence and high effect sizes for general ER deficits, such as awareness and acceptance of emotions, in patients with agoraphobia. These latter findings are in line with similar results in a sample of people who experience uncued panic attacks (Tull and Roemer 2007) and greater attempts to control emotional experiences and expression in patients with panic disorder (Baker et al. 2004). The absence of differences in ER strategy usage during stress in our sample, however, warrants closer scrutiny. Given the shortness and moderate internal consistency of the scales used, noisy data could mask existing differences between the groups. However, the effect of reduced reappraisal in the PA group found in the longer and well-established trait measure (ERQ) still does not align with established transdiagnostic findings (Aldao et al. 2010), which emphasize peculiarities in dysfunctional rather than functional ER strategies. It is also possible that the two strategies contrasted in our study (reappraisal and suppression) are not sufficient to cover the complexity of ER in the context of anxiety, where emotional acceptance, for example, is also supposed to play an important role (Hofmann et al. 2009). Furthermore, it is questionable whether reappraisal would indeed be an adaptive, and suppression a maladaptive ER response to our emergency stressor. While the established connection of reappraisal to an "adjusting", problem-solving affective style (Hofmann et al. 2012) supports this view, it can be argued that it is flexible usage of strategies (rather than features of the strategies themselves) that is adaptive (Bonanno et al. 2004), and an emergency might be a context where suppression is useful. Nonetheless, these two strategies have been demonstrated to be especially relevant in the context of panic (Levitt et al. 2004). Thus, one has to consider the possibility that patients with agoraphobia suffer more from a general sense of fearfulness and loss of control concerning emotional states (as measured by the DERS) than from dysfunctional ER strategies. This notion is supported by findings that a generalized fear of a range of positive and negative emotions (expanding on the concept of "fear of fear") is related to panic disorder (Williams et al. 1997). Interestingly, fear of bodily sensations has been shown to predict difficulties in ER measured by the DERS (Tull et al. 2008), supporting this idea and providing a link between the findings on ER and interoception. In this sense, it would be patients' perception of their feelings as dangerous and out of control rather than actual deficits in regulating emotions that characterize the disorder. This misguided perception, then, plausibly causes dysfunctional (avoidance-based) coping observed in patients with panic disorder (Feldner et al. 2004), which has been shown to aggravate panic symptoms (Kaplan et al. 2012). These findings, if confirmed by future research, lend support to the notion that exposure-based treatments could benefit from incorporating acceptance and mindfulness components (Treanor 2011), e.g. by making it easier to confront feared sensations (Eifert and Heffner 2003) and by enhancing the tolerance for negative emotional states (Arch and Craske 2006).

A number of limitations of the current study must be considered when interpreting the findings. Problems with our state measure of ER have already been discussed above. Furthermore, PA and HC groups differed substantially in age, even though not in gender composition. While an influence of age on tonic heart rate variability (and to a lesser extent heart rate) has been reported (Antelmi et al. 2004; Umetani et al. 1998), it is less clear how age should influence the psychophysiological reactivity central to our study, or our questionnaire data. We correlated age with all outcome variables separately in both groups and found no statistically significant correlations.[5] Taken together with the specificity of our findings for different branches of the autonomic nervous system and specific questionnaires, it is not plausible that age effects should explain a large part of this variance, and the comparisons of psychophysiological variables with their perception should be even more independent from age. Nonetheless, it would be important to replicate our results with a carefully matched control group. Also concerning the composition of our healthy control group, the decision to not determine their personality disorder status with SCID-II makes some interference possible, and should be improved upon in further studies.

[5] All $rs \leq .25$ with $ps \geq .2$ for psychophysiological variables, using difference scores from baseline to stressor. All $rs \leq .35$ with $ps \geq .08$ for self-report variables. No correction for multiple testing applied.

A further limitation concerns the composition of our patient group. While questionnaire data indicate that agoraphobic impairment was in the moderate to severe range, one has to assume that an outpatient sample such as ours differs from the more severely impaired patients that require inpatient treatment. Furthermore, while the focus of our study was on agoraphobia, DSM-IV diagnoses didn't permit to disentangle the relative importance of panic disorder and agoraphobia on the diagnostic level (as the newly introduced DSM-5 would). On the other hand, both PA and HC groups were assessed with the most rigorous clinical interview available (SCID), providing a valid sample characterization. The effects we found can be assumed to be more pronounced, if anything, in an inpatient sample. Relatedly, the influence of depressive symptomatology has to be considered in studies on panic disorder, as mood and anxiety disorders share significant variance (Kessler et al. 1998). As has to be expected, our PA and HC groups differed in depressive symptoms, limiting the attribution of our results to features of agoraphobia. The average degree of depressive symptoms according to BDI-II in the PA group was on the lower bound of "mild" depressive symptoms, however, and no participant fulfilled diagnostic criteria for any affective diagnosis. Thus, a substantial influence of features of depression on our results is not plausible.

Finally, the generalizability of our stressor scenario can be questioned. A fire in an underground parking garage is not an everyday occurrence, and only loosely related to agoraphobic situations. Furthermore, the fact that participants had some freedom of decision and movement in the VR environment reduces internal validity despite the relatively stringent scripting of events, as stimuli cannot be assumed to be identical at any given time. Nonetheless, we believe our stressor to be highly suitable in a number of ways. First, participants were forced to react within the scenario, which is an important feature of everyday emotional experience that is usually missing from emotion induction in the laboratory. Second, our scenario provoked similar levels of subjective anxiety in PA and HC groups, allowing valid comparisons between the other subjective and psychophysiological variables. Third, even though not purely agoraphobic in nature, the scenario incorporated important features relevant to agoraphobia: enclosed spaces (elevator and parking garage in the scenario), difficulty to escape from the situation underground, and the dark and enclosed laboratory itself. The stress and arousal participants experienced in the experiment can thus be assumed to resemble that from everyday situations. Still, a replication with different scenarios is desirable, possibly comparing the effects of nonspecific and agoraphobic stressors. The virtual reality scenario's efficacy in evoking emotional and psychophysiological responses from the participants is also in line with research on virtual reality exposure therapy (Powers and Emmelkamp 2008) and lends further support to this innovative therapeutic approach.

In summary, the limitations just discussed and the novelty of our findings regarding reduced psychophysiological reactivity and the absence of ER strategy differences in agoraphobia make this a preliminary study in need of replication. Nonetheless, this is the first study to our knowledge comparing psychophysiological, interoceptive and ER responses to an ecologically valid anxiety induction in an agoraphobic sample. The findings of exaggerated perception of bodily sensations despite reduced psychophysiological reactivity and broad sense of loss of control concerning one's own emotions without clear deficiencies in ER strategies could have important therapeutic implications. Apart from confirming cognitive therapy's work with catastrophic misinterpretations of bodily sensations, our results tentatively suggest that patients' existing resources in ER should be activated and possibly supplemented with exercises on the tolerance of emotions.

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Compliance with Ethical Standards

Conflict of Interest Christoph Breuninger, David M. Sláma, Martina Krämer, Julian Schmitz and Brunna Tuschen-Caffier declare that they have no conflict of interest.

Informed Consent All procedures performed involving human participants were approved by the University of Freiburg ethics committee (153/12) and in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Animal Rights This article does not contain any studies with animals performed by any of the authors.

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