



Metabolic decoupling in daily life in patients with panic disorder and agoraphobia



Monique C. Pfaltz^{a,1}, Vitaliy Kolodyazhnyi^{b,c,1}, Jens Blechert^b, Jürgen Margraf^d, Paul Grossman^e, Frank H. Wilhelm^{b,*}

^a Department of Psychiatry and Psychotherapy, University Hospital Zurich, Switzerland

^b Department of Psychology, Division of Clinical Psychology, Psychotherapy, and Health Psychology, University of Salzburg, Austria

^c Ziemer Ophthalmic Systems AG, Switzerland

^d Department of Clinical Psychology and Psychotherapy, Ruhr-University Bochum, Germany

^e Department of Psychosomatic Medicine, Division of Internal Medicine, University Hospital Basel, Basel, Switzerland

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ABSTRACT

Various studies have assessed autonomic and respiratory underpinnings of panic attacks, yet the psychophysiological functioning of panic disorder (PD) patients has rarely been examined under naturalistic conditions at times when acute attacks were not reported. We hypothesized that emotional activation in daily life causes physiologically demonstrable deviations from efficient metabolic regulation in PD patients. Metabolic coupling was estimated as within-individual correlations between heart rate (HR) and indices of metabolic activity, i.e., physical activity (measured by 3-axial accelerometry, Acc), and minute ventilation (Vm, measured by calibrated inductive plethysmography, as proxy for oxygen consumption). A total of 565 daytime hours were recorded in 19 PD patients and 20 healthy controls (HC). Pairwise cross-correlations of minute-by-minute averages of these metabolic indices were calculated for each participant and then correlated with several indices of self-reported anxiety. Ambulatory HR was elevated in PD ($p = .05$, $d = 0.67$). Patients showed reduced HR-Acc ($p < .006$, $d = 0.97$) and HR-Vm coupling ($p < .009$, $d = 0.91$). Combining Vm and Acc to predict HR showed the strongest group separation ($p < .002$, $d = 1.07$). Discriminant analyses, based on the combination of Vm and Acc to predict HR, classified 77% of all participants correctly. In PD, HR-Acc coupling was inversely related to trait anxiety sensitivity, as well as tonic and phasic daytime anxiety. The novel method that was used demonstrates that anxiety in PD may reduce efficient long-term metabolic coupling. Metabolic decoupling may serve as physiological characteristic of PD and might aid diagnostics for PD and other anxiety disorders. This measure deserves further study in research on health consequences of anxiety and psychosocial stress.

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1. Introduction

Numerous studies have assessed cognitive and physiological underpinnings of panic attacks (PAs) (Papp et al., 1993), but a clear understanding of panic disorder (PD) is still lacking. Moreover, it is questionable if laboratory findings can be generalized to patients' everyday life since PD patients are particularly sensitive to

experimental contexts (Abelson et al., 2007). Therefore, some studies have investigated PD patients in their daily lives. These studies found subtle but significant precursors of naturally occurring PAs in heart rate and other physiological measures (Margraf et al., 1987; Meuret et al., 2011). A rarely studied question relates to PD patients' psychophysiological functioning in the absence of PAs. Specifically, do PD patients show elevated physiological responses to challenges of daily life? Such responses would parallel subjective complaints about persistently elevated anxiety and arousal (Taylor et al., 1995; Brown et al., 2009). Furthermore, such background psychophysiological activation might provide a basis for PAs by lowering the threshold for acute panic (Clark, 1986; Ehlers et al., 1988). The present study was concerned with the assessment of such alterations.

* Corresponding author. University of Salzburg, Department of Psychology, Division of Clinical Psychology, Psychotherapy, and Health Psychology, Hellbrunnerstrasse 34, 5020 Salzburg, Austria. Tel.: +43 (0)662 8044 5103; fax: +43 (0)662 8044 5126.

E-mail address: frank.wilhelm@sbg.ac.at (F.H. Wilhelm).

¹ These two authors contributed equally to this paper.

One index of potential psychophysiological background activation in anxiety disorders is HR (Kreibig, 2010). HR is closely related to emotional processes: During intense anxiety, accelerations of up to 110 bpm have been observed (Wilhelm and Roth, 1998a). Laboratory studies demonstrated that HR elevations to acute threat are in excess of metabolic demand and beta-adrenergically mediated (Langer et al., 1979; Sherwood et al., 1986). Since much of HR variation across the day reflects movement related muscular activity, separation of metabolic and anxiety related contributions to HR is a challenge for ambulatory anxiety research. Thus, the concept of ‘additional HR’ was developed: sophisticated accelerometric measurements were used to index metabolic demand. HR acceleration in excess of these demands were considered anxiety related, additional HR (Myrtek et al., 1988). This approach has been expanded by measuring minute ventilation (Vm, the total amount of liters expired and inspired per minute) (Grossman et al., 2010; Wilhelm and Roth, 1998b). Here, we utilize both accelerometry and Vm to index metabolic contributions to HR.

In daily life, HR and Vm are strongly coupled to physical activity since muscular work and the associated increased metabolism require increased oxygen transport. Generally, at low to moderate levels of aerobic exercise, which correspond well with people's daily routines, both HR and Vm increase rather linearly to transport oxygen to muscles and organs (Delistraty et al., 1991). At these levels, Vm is a good proxy for oxygen consumption, a putative index of metabolic activity (Grossman et al., 2010). Compared to HR, Vm is less tightly coupled to emotional activation (Delistraty et al., 1991; Wilhelm et al., 2006). Nevertheless, anxiety and PD have been associated with respiratory alterations. For example, variability indices (Wilhelm et al., 2001a) and sigh rate (Wilhelm et al., 2001b) but also lowered end-tidal partial CO₂ pressure were repeatedly found in PD (Papp et al., 1997; Hegel et al., 1997). However, in line with other studies showing that hyperventilation plays some, but not a major role in anxiety (Wilhelm and Roth, 1998a; Kreibig, 2010; Garssen et al., 1996), ambulatory recordings of respiratory pattern in PD found no evidence for trait-abnormalities in breathing – not in terms of respiratory timing and respiratory volume parameters and neither during minimal physical activity (Pfaltz et al., 2009) nor during different levels of physical activity (Pfaltz et al., 2010b). Vm might therefore be considered a relatively anxiety-independent index of metabolic demand, especially in ambulatory studies. In daily life of PD patients, elevated anxiety (outside PAs) should thus result in HR increases but also in *decoupling between physical activity and HR*, due to emotion related HR changes, occurring in excess of metabolically related HR alterations (Wilhelm and Roth, 1998b; Carroll et al., 1986). Conversely, coupling between physical activity and Vm should be relatively unaffected by anxiety, as Vm is strongly related to physical activity but only weakly to anxiety. Thus, elevated anxiety in PD should also reduce coupling between HR and Vm.

We assessed this anxiety-related decoupling between physical activity and HR and between Vm and HR in daily life of PD patients and healthy controls (HC). We assumed that assessment of metabolic coupling would reveal physiological alterations in PD that, with traditional methods, were only detectable in some (Martinez et al., 1986; Stein et al., 1995) but not in other ambulatory studies (Hoehn-Saric et al., 2004; Pfaltz et al., 2009, 2010b). More specifically, we assumed that PD patients show elevated and more frequent *phasic* anxiety reactions to daily situations (Pfaltz et al., 2010a) that might be accompanied by HR fluctuations that are disproportional to metabolic demands. This would give rise to a) elevated HR and b) decoupling between HR and accelerometry and between HR and Vm. Second, we assumed that PD patients show elevated trait anxiety and anxiety sensitivity (McNally, 1999), resulting in elevated *tonic* emotional activation and

associated trait-like, anxiety related physiological changes like persistent HR elevations (Hoehn-Saric et al., 1991; Martinez et al., 2010; Roth et al., 1986; Cohen et al., 2000). Such persistent changes might interfere with the fine tuning between organismic systems that are normally efficiently and rapidly coupled via feedback loops during periods of varying physical activity, further diminishing associations between HR and accelerometry and between HR and Vm. We thus assessed the hypotheses that 1) PD patients show diminished coupling between HR and accelerometry and between HR and Vm and that 2) In PD, HR-Acc coupling and HR-Vm coupling are inversely related to both phasic and tonic anxiety.

2. Material and methods

2.1. Participants

Participants were recruited as part of a larger study assessing anxiety symptoms (Pfaltz et al., 2010a, 2013) and ambulatory respiratory measurements (Pfaltz et al., 2009, 2010b). For the present analyses, we included 19 PD patients and 20 HC of the original sample (Pfaltz et al., 2009) who, in addition to undergoing physiological monitoring, completed electronic symptom diaries (Pfaltz et al., 2010a), providing information on anxiety and PAs. All PD patients were additionally diagnosed with agoraphobia. Other comorbidities were major depression (n = 2), social phobia (n = 2), and primary insomnia (n = 1). Exclusion criteria were significant hypertension, respiratory or cardiocirculatory diseases, and medication with strong autonomic effects. All HC were medication free. Six PD patients received one or more medications (4 of these patients received selective serotonin reuptake inhibitors, 1 received benzodiazepines, and 1 received benzodiazepines, a noradrenergic and specific serotonergic antidepressant, and antihypertensive medication from the class of angiotensin II receptor antagonists). Study groups were matched for age, gender, and BMI (Table 1). PD patients showed heightened anxiety sensitivity and trait anxiety (Table 1).

2.2. Procedure

The study was approved by the medical ethics committee of Basel, Switzerland. After providing informed consent, participants were interviewed with the German Anxiety Disorders Interview Schedule for DSM-IV (DiNardo et al., 1994; Schneider and Margraf, 2006). Eligible participants returned to a second laboratory visit, starting at 8.30 am. Participants were instrumented and after

Table 1
Participant characteristics and self-report measures of anxiety for panic disorder (PD) patients and healthy controls (HC).

	PD (n = 19)	HC (n = 20)	*p
	Mean ± SD	Mean ± SD	
Age	32.84 ± 9.65	35.05 ± 8.33	0.45
Sex (N, % female)	16 (84%)	16 (80%)	**0.73
Body mass index	24.24 ± 4.25	22.86 ± 3.59	0.30
<i>Tonic anxiety</i>			
Mean anxiety ^a	2.18 ± 1.31	0.04 ± 0.12	<0.001
STAI-Trait ^b	48.86 ± 3.26	40.53 ± 3.81	<0.001
ASI ^b	26.87 ± 8.70	6.21 ± 3.26	<0.001
<i>Phasic anxiety</i>			
SD anxiety ^a	1.60 ± 0.75	0.05 ± 1.69	<0.001

Note: *p value corresponds to t-test unless indicated otherwise; **p value corresponds to χ^2 test; BDI, Beck Depression Inventory; STAI-Trait, State Trait Anxiety Inventory (trait scale); ASI, Anxiety Sensitivity Index.

^a Assessed by electronic diary.

^b Assessed by trait questionnaires.

completing a 2-min quiet sitting baseline, they pursued their daily routine for the next 24 h. Additionally, they were shown how to use the electronic diary to record PAs and other symptoms during the coming week. Participants completed another 24 h physiological recording one week later. Participants were instructed not to do sports exercises or to pursue exhausting physical activities during recordings.

2.3. Physiological data collection

We used the LifeShirt (VivoMetrics, Inc., Ventura, USA) to obtain ambulatory physiologic measures. The LifeShirt continuously measured physical activity, i.e. direction and intensity of acceleration, in three spatial axes with an accelerometer placed at the level of the sternum (sample rate: 10 Hz). Three electrodes, placed on upper chest and lateral surface of abdomen, sampled a lead-II ECG (200 Hz). Respiratory waveforms were sampled at 50 Hz from two inductive plethysmography sensors placed around abdomen and chest.

2.4. Physical fitness test

To assure that the hypothesized metabolic coupling group differences are unrelated to physical fitness group differences, participants were asked to, before leaving the laboratory, sit quietly for 2 min and then to walk at slow, intermediate, and fast paces at standardized speeds for 3 min. We calculated a composite physical fitness index that includes participants' sex, as well as slope and intercept from the linear prediction of heart rate by means of accelerometry during this task. This index shows good agreement ($R^2 = 0.90$) with the gold-standard assessment of physical fitness, maximal oxygen consumption during incremental exercise (Tönis et al., 2012).

2.5. Panic attacks and measures of phasic and tonic anxiety

2.5.1. Panic attacks

Starting on the first physiological measurement day, participants completed an electronic diary during one week. Diary questions were programmed by Pendragon Forms (Pendragon Software Corporation, Libertyville, USA) and installed on Palm Tungsten E handheld computers (Pfaltz et al., 2010a, 2013). Participants were prompted to complete the diary at 9 am, 12 pm, 3 pm, 6 pm, and 9 pm. They rated their mood and various symptoms of panic and anxiety with respect to the past three hours or – at 9 am – with respect to the time since waking up. Additionally, participants completed the diary any time they experienced PAs.

PAs were defined as follows: 1. Participants reported a PA. 2. They reported four or more of the 13 DSM-IV symptoms of PAs (dichotomous items). 3. Anxiety, which was rated on a 0 (not at all) to 10 (very much) Likert-scale increased 1 or more units from the preceding entry. We excluded periods with PAs from the data analyses, since we were interested in trait-like psychophysiological background activation.

2.5.2. Tonic anxiety

Trait anxiety was measured by three variables: 1. By the averaged diary-reported anxiety levels on the physiological monitoring day. 2. By the trait part of the German State-Trait Anxiety Inventory (Laux et al., 1981). 3. By the German Anxiety Sensitivity Index (Reiss et al., 1986).

2.5.3. Phasic anxiety

The standard deviation (SD) of diary-reported anxiety levels on the physiological monitoring day served as index of phasic anxiety, as it reflects the degree to which anxiety levels vary across the day.

2.6. Physiological data processing and statistical analyses

Four PD patients reported one or more PAs during the first physiological recording. For these participants, we used data of the second recording. For all remaining participants, we used data of the first recording. Only data collected during waking periods were included because of the complexities of sleep determination and sleep behavior and because we were interested in the relationship of self-reported anxiety and physiological functioning. Sleep onset and end of sleep were determined by visual inspection of activity and respiration parameters around typical bed times using the following criteria: the beginning of the first 15-min interval with supine position, minimal accelerometry activity, and regular respiration that was followed by several such inactivity periods was taken as sleep onset, the beginning of a 15 min interval with irregular respiration and activity, that was followed by several such activity periods served as approximate marker of end of sleep.

Recordings started between 7:50 am and 10:40 am and ended between 11:40 pm and 10:11 am. In total, the analyzed waking data comprised approximately 565 h (ca. 34,000 minute-by-minute averages for all monitored variables). Average duration of waking data was 888.7 ± 105.1 min for PD patients and 850.0 ± 88.21 min for HC ($p < .22$). Minute-by-minute averaging of beat-by-beat HR time-series and breath-by-breath Vm time-series was done via one-minute medians, minimizing the effect of outliers and improving robustness against measurement artifacts.

We used the Vivologic[®] software to edit artifacts, calibrate respiratory channels, and compute Vm, HR, and physical activity. Data of the three physical activity channels were summed to obtain a whole body accelerometry motion index (Acc), reflecting intensity of physical activity. Beat-by-beat HR was calculated by Vivologic after removing measurement artifacts and replacing them by linear interpolation. We used qualitative diagnostic calibration (Sackner et al., 1989) to set proportional gains of the respiratory sensors. Respiratory waveforms were added and absolute tidal volume (Vt) was calculated in ml by applying a calibration procedure conducted during set-up of the measurements (participants rebreathed into a 750 ml plastic bag for 8 times; this was repeated after a pause). Minute ventilation (Vm, liters/min) was calculated breath-by-breath $[Vm = (Vt \cdot 60) / (\text{breath duration [in sec]}) \cdot 1000]$.

For participant's complete waking data, within-individual pairwise Pearson correlations of minute-by-minute averages $r(\text{HR-Acc})$, $r(\text{Vm-Acc})$, and $r(\text{HR-Vm})$ were calculated as univariate indices of metabolic coupling. The product moment correlation was chosen as measure of metabolic coupling as we aimed at developing a simple measure also applicable to clinical settings. However, since HR is not only driven by current activity but also by activity of the preceding minutes, differential autocorrelation patterns may influence these cross-correlational results. To exclude this possibility, we calculated (Fisher transformed) autocorrelations for the HR time series. These were highly comparable between groups (mean (SD) for PD: $r = .859$ (.042), HC: $r = .858$ (.045), $p = .91$, $d = 0.04$). Similarly, groups did not differ in autocorrelations for the Vm and Acc data (p values $> .21$, effect sizes d range between 0.22 and 0.42). Additionally, we computed multiple correlation of HR with Acc and Vm, $r[\text{HR-(Acc,Vm)}]$, as bivariate index of metabolic coupling. The latter was a Pearson correlation of HR with predicted HR via linear least-square-based multiple regression, using predictors Vm and Acc.

To assess whether the expected elevated HR and diminished metabolic coupling in PD were related to tonic and/or phasic anxiety, mean HR and Fisher Z-transformed indices of metabolic coupling were Pearson correlated with SD of diary-reported anxiety, mean diary-reported anxiety, STAI and ASI scores within PD patients.

We used *t*-tests to compare study groups. Additionally, we performed discriminant analysis on three indices of metabolic coupling, $r(\text{HR-Acc})$, $r(\text{HR-Vm})$, and $r[\text{HR-(Acc,Vm)}]$, to assess group discriminability in terms of classification accuracy. We used in-sample analyses for fitting discriminant functions and computing the classification rate, based on each metabolic coupling index separately (univariate discriminants) and on the combined variables $r(\text{HR-Acc})$ and $r(\text{HR-Vm})$, using bivariate linear and quadratic discriminants. For the three best classification models, we additionally performed leave-one-out cross-validation (Hastie et al., 2001) to estimate classification accuracy for out-of-sample data. All discriminant analyses were computed using Fisher Z-transformed correlations.

3. Results

Groups did not differ in age, gender, or BMI but patients showed elevated tonic and phasic anxiety (Table 1).

Groups were comparable regarding mean Acc and Vm. PD patients had higher mean HR than HC (Table 2). When including Acc as covariate, this group difference was no longer significant ($F(1,35) = 3.36, p = .075$). For Vm, when including Acc as covariate, no significant group difference emerged ($F(1,35) = 0.58, p = .45$). Acc-HR and Vm-HR coupling was lower in PD than in HC. When using Acc and Vm in conjunction to predict HR, diminished coupling in PD patients was even more pronounced (see effect size, Table 2). Group differences in metabolic coupling indices remained significant after excluding medicated patients (p values $< .011$).

Since PD patients displayed elevated HR, we assessed whether metabolic coupling indices were redundant to mean HR. In both groups, mean HR was unrelated to HR-Acc coupling (PD: $r = -.01, p = .96$; HC: $r = .10, p = .67$) and to HR-(Acc,Vm) coupling (PD: $r = -.22, p = .36$; HC: $r = -.38, p = .10$). In HC ($r = -.46, p = .044$) but not in PD patients ($r = -.31, p = .20$), higher HR was associated with diminished Vm-HR coupling. In PD, none of the correlations between mean HR and measures of tonic and phasic anxiety reached significance (p values $> .26$), yet Acc-HR was negatively correlated with ASI scores ($r = -.583, p = .023$), mean ($r = -.464, p = .045$) and SD ($r = -.461, p = .047$) of diary-reported anxiety.

Discriminant analysis suggested better discriminatory power of the HR-Acc than the HR-Vm coupling index (see Table 2, effect sizes). Regarding in-sample analyses, a linear discriminant classifier with a single predictor $r(\text{HR-Acc})$ correctly assigned 29 participants (74.36%) to their study group. Four HC (10.26%) and 6 patients

(15.38%) were misclassified. Classification based on $r(\text{HR-Vm})$ correctly assigned 27 study participants (69.23%). Six HC and 6 patients (both 15.38%) were misclassified. Classification based on multiple correlation $r[\text{HR-(Acc,Vm)}]$ assigned 25 participants correctly (64.10%). Eight HC (20.51%) and 6 patients (15.38%) were misclassified.

A bivariate linear discriminant classifier including the individual variables $r(\text{HR-Acc})$ and $r(\text{HR-Vm})$ correctly classified 27 participants (69.23%). Six HC and 6 patients (both 15.38%) were misclassified. A bivariate quadratic discriminant classifier with predictors $r(\text{HR-Acc})$ and $r(\text{HR-Vm})$ classified 30 participants (76.92%) correctly. Two HC (5.13%), and 7 patients (17.95%) were misclassified.

For the three best-performing classifiers we also computed out-of-sample analysis in form of leave-one-out cross-validation. For the univariate linear classifier with the predictor $r(\text{HR-Acc})$, leave-one-out cross-validation and in-sample test revealed identical results, indicating substantial robustness of the classification algorithms. For the linear discriminant classifier based on the predictor $r(\text{HR-Vm})$, one more PD patient was misclassified in the leave-one-out setting (26 correctly classified participants, or 66.67%). Among the 13 misclassified participants 6 were HC (15.38%) and 7 patients (17.95%). For the bivariate quadratic discriminant classifier with predictors $r(\text{HR-Acc})$ and $r(\text{HR-Vm})$, one more control and one more PD patient were misclassified compared to in-sample classification: 28 participants (71.79%) were correctly classified. Three HC (7.69%) and 8 patients (20.51%) were misclassified. Except for the indicated additional misclassified participants, all other correctly and incorrectly classified and misclassified HC and PD were the same for in-sample and out-of-sample analyses for all the three best-performing classification models. Furthermore, the same 5 participants (1 HC and 4 PD) were misclassified in both in-sample and out-of-sample settings by all the three best classifiers. This comprises 12.28% participants in total, or 38.46%–55.55% of all misclassifications for the respective analysis and classifier.

Fig. 1 shows distribution of study participants according to their metabolic coupling indices, as well as the cut-off scores and the decision boundary of in-sample classification for the three best-performing classifiers. The single HC misclassified in all classification runs is represented by the circle in the bottom left corner, surrounded by asterisks (PD patients). In turn, the four PD patients misclassified in all runs are the four asterisks in the upper right quadrant above the cut-off score for the linear classifier based on the variable $r(\text{HR-Acc})$, and to the right of the cut-off score for the classifier based on $r(\text{HR-Vm})$.

Physical fitness indices did not differ between groups ($p = .56$). Group differences in metabolic coupling indices $r(\text{HR-Acc})$, $r(\text{Vm-Acc})$, and $r[\text{HR-(Acc,Vm)}]$ remained significant when using physical fitness as covariate (p values $< .015$).

Table 2
Means (SD) for physiological variables and metabolic coupling indices for PD patients and HC.

Measure	PD (n = 19)	HC (n = 20)	T-test		
	Mean ± SD	Mean ± SD	<i>p</i>	<i>df</i>	<i>d</i>
<i>Average levels</i>					
HR (beats/min)	87.46 ± 9.53	81.84 ± 7.58	0.048*	37	0.67
Vm (l/min)	10.38 ± 4.92	9.35 ± 2.84	0.43	37	0.26
Acc (g)	0.888 ± 0.473	1.021 ± 0.464	0.38	37	0.29
<i>Metabolic coupling indices</i>					
$r(\text{HR-Acc})$	0.632 ± 0.058	0.682 ± 0.049	0.005**	37	0.97
$r(\text{Vm-Acc})$	0.710 ± 0.081	0.704 ± 0.104	0.90	37	0.04
$r(\text{HR-Vm})$	0.675 ± 0.096	0.754 ± 0.084	0.009**	37	0.91
$r[\text{HR-(Acc,Vm)}]$	0.717 ± 0.078	0.790 ± 0.064	0.002**	37	1.07

Note: HR, heart rate; Acc, accelerometry; Vm, minute ventilation; *d*, Cohen's effect size for group comparisons, * $p < .05$, ** $p < .01$.

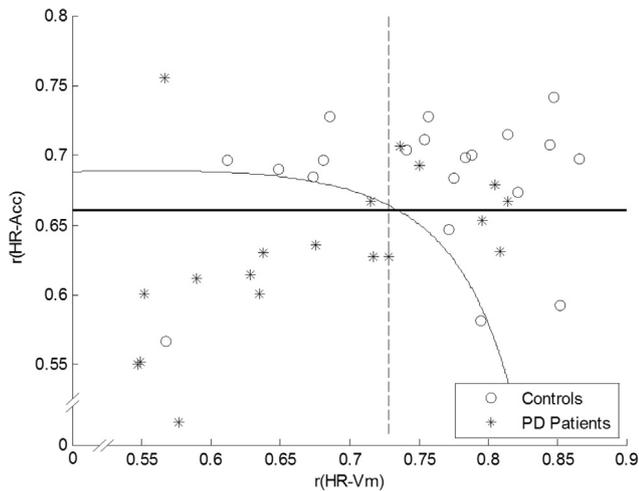


Fig. 1. Distribution of study participants according to their metabolic coupling indices. The horizontal thick line represents the cutoff score of 0.66 for the best linear discriminant classifier based on the variable $r(\text{HR-Acc})$, the dashed vertical line is the cutoff score of 0.73 for the linear discriminant classifier based on the variable $r(\text{HR-Vm})$, and the thin curve is the decision boundary for the bivariate quadratic discriminant classifier. Raw Pearson r values are shown to facilitate interpretation, while the respective discriminant analyses were computed using Fisher Z -transformed Pearson r values. Lower coupling levels on both axes are primarily associated with PD.

4. Discussion

We used a novel approach to examine metabolic indices and emotional activation in PD patients in daily life. In line with our hypotheses, considering ventilation and accelerometry separately as metabolic activity markers reliably revealed reduced coupling of these indices with HR in PD relative to HC. When combining the two, the effect size for the group difference in metabolic coupling was even higher, suggesting that accelerometry and minute ventilation are both important, non-redundant variables for assessing ambulatory HR alterations in PD. In line with this finding, discriminant analyses using a bivariate quadratic discriminant classifier suggest a benefit of classification models that combine the metabolic indices $r(\text{HR-Acc})$ and $r(\text{HR-Vm})$ for diagnostic purposes. Based on this model, 77% of participants were classified correctly.

Conversely, coupling between accelerometry and minute ventilation was highly comparable between study groups. This is in line with our supposition and research showing that minute ventilation is closely related to oxygen consumption (Delistraty et al., 1991; Grossman et al., 2010) but only weakly to anxiety (Wilhelm et al., 2006). It also corroborates ambulatory studies which, against theories of chronic hyperventilation in PD (Klein, 1993), found no evidence for respiratory patterns that would suggest a tendency of PD patients to breathe in excess to metabolic demands in their daily lives, neither in terms of respiratory timing nor respiratory volume parameters (Pfaltz et al., 2009, 2010b).

In line with some (Hoehn-Saric et al., 1991; Martinez et al., 2010; Roth et al., 1986; Cohen et al., 2000) but not with other studies (Hoehn-Saric et al., 2004; Clark et al., 1990; Yeragani et al., 1998), PD patients had higher ambulatory HR than HC, although this difference disappeared when partialling out average physical activity. In HC, higher average HR was associated with diminished coupling between Vm and HR, with a shared variance of 21%. On the other hand, average HR was unrelated to coupling between Vm and HR in PD, indicating that the observed metabolic decoupling is a novel marker that needs to be considered separately from simple HR elevations. Furthermore, while previous research indicates that PD patients might be less physically fit than healthy controls (Taylor

et al., 1987), we found no evidence for reduced physical fitness in our sample of PD patients. In addition, group differences in metabolic decoupling remained significant after covarying out the effect of physical fitness. Metabolic decoupling in our PD sample thus seems not simply attributable to diminished physical fitness.

Negative associations between metabolic coupling and measures of phasic and tonic anxiety in PD support our assumption that PD patients show psychophysiological hyperactivation, even outside acute panic. Furthermore, the negative association between metabolic coupling and anxiety variability corroborates the idea that PD patients are hypersensitive towards environmental stimuli that activate the sympatho-adrenal medullary axis (Abelson et al., 2007). It also extends previous findings of enhanced variability of anxiety symptoms in PD (Pfaltz et al., 2010a) by showing that in PD, variability of self-reported anxiety is related to HR alterations in daily life. The association between anxiety sensitivity and metabolic decoupling suggests that it might be worthwhile to assess not only psychological but also physiological, adverse effects of a generalized fear of anxiety related symptoms. However, we cannot rule out that metabolic decoupling in PD is related to nonpsychological factors such as neurometabolic abnormalities. For example, there is evidence that PD patients show increased brain lactate responses to neural activation that seem to be a trait feature of PD. Increased brain lactate accumulation might, in turn, be related to abnormalities in acid-sensitive circuits that are associated with autonomic, respiratory, and fear-related processing (Maddock et al., 2013).

A limitation of our study is that group differences in frequency and duration of specific types of activities (which we did not assess) may have confounded the relationship between accelerometry and heart rate. For example, agoraphobic PD patients may be more likely to stay near home and to avoid exercise, which may have resulted in reduced muscular work and thus in reduced heart rate fluctuations and lower coupling between accelerometry and heart rate. However, participants were instructed not to pursue exhausting physical activities and groups did not differ in average accelerometry levels. Also, PD patients did not differ from healthy controls in the amount of time spent at different levels of physical activity (Pfaltz et al., 2010b). We therefore assume that both study groups had a similar and sufficient variance in the variables used for metabolic coupling computations. Nevertheless, future studies should assess physical and other activities (e.g., talking; Wilhelm et al., 2003) that can influence HR independently of emotional arousal (Sloan et al., 1991). Finally, ambulatory additional HR was not computed directly because this would require an anxiety-free baseline exercise calibration as was done in patients with specific phobia (Wilhelm and Roth, 1998b). PD patients differ from specific phobia patients as they experience more tonic background anxiety (Taylor et al., 1995; Brown and McNiff, 2009), and experience particularly elevated anxiety during baseline laboratory assessments (Wilhelm et al., 2001a).

It would be of interest to assess whether reduced metabolic coupling in PD is also present during sleep. If reduced metabolic coupling is a biological trait, it might not be restricted to waking hours. Unfortunately, we were unable to explore this possibility as HR varies significantly with different sleep stages (Aldredge and Welch, 1973) and we did not obtain polysomnographic measurements that are necessary to reliably distinguish different sleep stages. Another weakness of our study is that while the standard approach to measuring physical fitness is to carry out a maximum aerobic exercise test (Buchfuhrer et al., 1983) our walking fitness test only provides a surrogate marker for physical fitness. We therefore can only provide indirect evidence for the absence of group differences in physical fitness. Nevertheless, group differences in physical fitness were far from significant. Also, differences in physical fitness

would primarily affect the steepness of the regression slope between accelerometry and HR, but not the extent of scatter that we primarily captured in our correlational coupling index.

Summing up, our measure of metabolic coupling has potential for discriminating between healthy individuals and PD patients. Reduced metabolic coupling in daily life might serve as marker for PD and, potentially, as marker for other conditions characterized by hyperarousal or elevated mental stress. In a nonclinical study (Kupper et al., 2005), common genes accounted for large parts of the covariance between ambulatorily recorded respiratory and cardiovascular parameters. Metabolic decoupling in PD might thus be worth evaluating as endophenotype by genetic studies. Also, future research could assess whether anxiety related metabolic decoupling might be mediated by abnormal connectivity and activation of limbic structures (Beutel et al., 2010; Pannekoek et al., 2013). Finally, persistent metabolic decoupling might be an important index of organismic allostatic load (McEwen, 1998), deserving further study in research on health consequences of negative affect and psychosocial stress (Kubzansky et al., 2002; Vanitallie et al., 2002).

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Contributors

Frank H. Wilhelm, Monique C. Pfaltz, Jens Blechert, Juergen Margraf, and Paul Grossman contributed to designing the study and drafting the manuscript. Data were analyzed by Monique C. Pfaltz and Vitaliy Kolodyazhnyi. All authors approved the final version of the manuscript.

Conflicts of interest

None of the authors have any biomedical, financial, or other conflicts of interest.

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References

- Abelson JL, Khan S, Liberzon I, Young EA. HPA axis activity in patients with panic disorder: review and synthesis of four studies. *Depress Anxiety* 2007;24:66–76.
- Aldredge JL, Welch AJ. Variations of heart rate during sleep as a function of the sleep cycle. *Electroencephalogr Clin Neurophysiol* 1973;35:193–8.
- Beutel ME, Stark R, Pan H, Silbersweig D, Dietrich S. Changes of brain activation pre-post short-term psychodynamic inpatient psychotherapy: an fMRI study of panic disorder patients. *Psychiatry Res* 2010;184:96–104.
- Brown TA, McNiff J. Specificity of autonomic arousal to DSM-IV panic disorder and posttraumatic stress disorder. *Behav Res Ther* 2009;47:487–93.
- Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol Respir Environ Exerc Physiol* 1983;55:1558–64.
- Carroll D, Turner JR, Hellaewell JC. Heart rate and oxygen consumption during active psychological challenge: the effects of level of difficulty. *Psychophysiology* 1986;23:174–81.
- Clark MD. A cognitive approach to panic. *Behav Res Ther* 1986;24:461–70.
- Clark DB, Taylor CB, Hayward C, King R, Margraf J, Ehlers A, et al. Motor activity and tonic heart rate in panic disorder. *Psychiatry Res* 1990;32:45–53.
- Cohen H, Benjamin J, Geva AB, Matar MA, Kaplan Z, Kotler M. Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of

- power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Res* 2000;96:1–13.
- Delistraty DA, Greene WA, Carlberg KA, Raver KK. Use of graded exercise to evaluate physiological hyperreactivity to mental stress. *Med Sci Sports Exerc* 1991;23(4):476–81.
- DiNardo PA, Brown TA, Barlow DH. Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version (ADIS-IV-L). Albany, NY: Graywind; 1994.
- Ehlers A, Margraf J, Roth WT. Selective information processing, interoception, and panic attacks. In: Hand I, Wittchen H-U, editors. *Panic and phobias*, Vol. 2. Berlin: Springer; 1988. p. 1299148.
- Garsen B, Buikhuisen M, van Dyck R. Hyperventilation and panic attacks. *Am J Psychiatry* 1996;153:513–8.
- Grossman P, Wilhelm FH, Brutsche M. Accuracy of ventilatory measurement employing ambulatory inductive plethysmography during tasks of everyday life. *Biol Psychol* 2010;84(1):121–8.
- Hastie T, Tibshirani R, Friedman J. The elements of statistical learning: data mining, inference, and prediction. New York: Springer-Verlag; 2001.
- Hegel MT, Ferguson RJ. Psychophysiological assessment of respiratory function in panic disorder: evidence for a hyperventilation subtype. *Psychosom Med* 1997;59:224–30.
- Hoehn-Saric R, McLeod DR, Zimmerli WD. Psychophysiological response patterns in panic disorder. *Acta Psychiatr Scand* 1991;83:4–11.
- Hoehn-Saric R, McLeod DR, Funderburk F, Kowalski P. Somatic symptoms and physiologic responses in generalized anxiety disorder and panic disorder: an ambulatory monitor study. *Arch Gen Psychiatry* 2004;61(9):913–21.
- Klein D. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. *Arch Gen Psychiatry* 1993;50:306–17.
- Kreibig SD. Autonomic nervous system activity in emotion – a review. *Biol Psychol* 2010;84:394–421.
- Kubzansky LD, Kawachi I. Going to the heart of the matter: do negative emotions cause coronary heart disease? *J Psychosom Res* 2002;48(4–5):323–37.
- Kupper N, Willemsen G, Posthuma D, de Boer D, Boomsma DI, de Geus EJ. A genetic analysis of ambulatory cardiorespiratory coupling. *Psychophysiology* 2005;42(2):202–12.
- Langer AW, Obrist PA, McCubbin JA. Hemodynamic and metabolic adjustments during exercise and shock avoidance in dogs. *Am J Physiol* 1979;236(2):H225–30.
- Laux L, Glanzmann P, Schaffner P, Spielberger CD. Das State-Trait-Angstinventar (STAI) [State–Trait Anxiety Inventory (STAI)]. Weinheim, Germany: Beltz; 1981.
- Maddock RJ, Buonocore MH, Miller AR, Yoon JH, Soosman SK, Unruh AM. Abnormal activity-dependent brain lactate and glutamate+glutamine responses in panic disorder. *Biol Psychiatry* 2013;73:1111–9.
- Margraf J, Taylor B, Ehlers A, Roth WT, Agras WS. Panic attacks in the natural environment. *J Nerv Ment Dis* 1987;175(9):558–65.
- Martinez JM, Garakani A, Kaufmann H, Aaronson CJ, Gorman JM. Heart rate and blood pressure changes during autonomic nervous system challenge in panic disorder patients. *Psychosom Med* 2010;72(5):442–9.
- Martinez JM, Papp LA, Coplan JD, Anderson EE, Mueller CM, Klein DF, et al. Ambulatory monitoring of respiration in anxiety. *Anxiety* 1986;2:296–302.
- McEwen BS. Stress, adaptation, and disease: allostasis and allostatic load. *Ann N Y Acad Sci* 1998;840:33–44.
- McNally RJ. Theoretical approaches to the fear of anxiety. In: Taylor S, editor. *Anxiety sensitivity: theory, research, and treatment of the fear of anxiety*. Mahwah, New Jersey: Lawrence Erlbaum Associates; 1999. p. 3–16.
- Meuret AE, Rosenfield D, Wilhelm FH, Zhou E, Conrad A, Ritz T, et al. Do unexpected panic attacks occur spontaneously? *Biol Psychiatry* 2011;70(10):985–91.
- Myrtek M, Bruegner G, Fichtler A, König K, Müller W, Foerster F, et al. Detection of emotionally induced ECG changes and their behavioural correlates: a new method for ambulatory monitoring. *Eur Heart J* 1988;9:55–90.
- Pannekoek JN, Veer IM, van Tol M-J, van der Werf SJA, Demenescu LR, Aleman A, et al. Aberrant limbic and salience network resting-state functional connectivity in panic disorder without comorbidity. *J Affect Disord* 2013;145:29–35.
- Papp LA, Klein DF, Gorman. Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. *Am J Psychiatry* 1993;150(8):1149–57.
- Papp LA, Martinez JM, Klein DF, Coplan JD, Norman RG, Cole R, et al. Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. *Am J Psychiatry* 1997;154:1557–65.
- Pfaltz MC, Grossman P, Michael T, Margraf J, Wilhelm FH. Physical activity and respiratory behavior in daily life of patients with panic disorder and healthy controls. *Int J Psychophysiol* 2010b;78:42–9.
- Pfaltz MC, Michael T, Grossman P, Blechert J, Wilhelm FH. Respiratory pathophysiology of panic disorder: an ambulatory monitoring study. *Psychosom Med* 2009;71:869–76.
- Pfaltz MC, Michael T, Grossman P, Margraf J, Wilhelm FH. Instability of physical anxiety symptoms in daily life of patients with panic disorder and patients with posttraumatic stress disorder. *J Anxiety Disord* 2010a;24:792–8.
- Pfaltz MC, Michael T, Meyer HA, Wilhelm FH. Reexperiencing symptoms, dissociation, and avoidance behaviors in daily life of patients with posttraumatic stress disorder and patients with panic disorder and agoraphobia. *J Trauma Stress* 2013;26:443–50.
- Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther* 1986;4:1–8.
- Roth WT, Telch MJ, Taylor CB, Sachitano JA, Gallen CC, Kopell ML, et al. Autonomic characteristics of agoraphobia with panic attacks. *Biol Psychiatry* 1986;21(12):1133–54.

- Sackner M, Watson H, Belsito A, Feinerman D, Suarez M, Gonzalez G, et al. Calibration of respiratory inductive plethysmograph during natural breathing. *J Appl Physiol* 1989;66(1):410–20.
- Schneider S, Margraf J. Diagnostisches Interview bei psychischen Störungen (DIPS). Berlin: Springer; 2006.
- Sherwood A, Allen MT, Obrist PA, Langer AW. Evaluation of beta-adrenergic influences on cardiovascular and metabolic adjustments to physical and psychological stress. *Psychophysiology* 1986;23(1):89–104.
- Sloan RP, Korten JB, Myers MM. Components of heart rate reactivity during mental arithmetic with and without speaking. *Physiol Behav* 1991;50:1039–45.
- Stein MB, Miller TW, Larsen DK, Kryger MH. Irregular breathing during sleep in patients with panic disorder. *Am J Psychiatry* 1995;152:1168–73.
- Taylor CB, King R, Ehlers A, Margraf J, Clark D, Roth WT, et al. Treadmill exercise test and ambulatory measures in patients with panic attacks. *Am J Cardiol* 1987;60:48–52.
- Taylor S. Anxiety sensitivity: theoretical perspectives and recent findings. *Behav Res Ther* 1995;33(3):243–58.
- Tönis TM, Gortler K, Vollenbroek-Hutten MM, Hermens H. Comparing VO₂max determined by using the relation between heart rate and accelerometry with submaximal estimated VO₂max. *J Sports Med Phys Fitness* 2012;52:337–43.
- Vanitallie TB. Stress: a risk factor for serious illness. *Metabolism* 2002;51:40–5.
- Wilhelm FH, Handke EM, Roth WT. Detection of speaking with a new respiratory inductive plethysmography system. *Biomed Sci Instrum* 2003;39:136–41.
- Wilhelm FH, Pfaltz MC, Grossman P, Roth WT. Distinguishing emotional from physical activation in ambulatory psychophysiological monitoring. *Biomed Sci Instrum* 2006;42:458–63.
- Wilhelm FH, Roth WT. Taking the laboratory to the skies: ambulatory assessment of self-report, autonomic, and respiratory responses in flying phobia. *Psychophysiology* 1998a;35:596–606.
- Wilhelm FH, Roth WT. Using minute ventilation for ambulatory estimation of additional heart rate. *Biol Psychol* 1998b;49:137–50.
- Wilhelm FH, Trabert W, Roth WT. Physiologic instability in panic disorder and generalized anxiety disorder. *Biol Psychiatry* 2001a;49:596–605.
- Wilhelm FH, Trabert W, Roth WT. Characteristics of sighing in panic disorder. *Biol Psychiatry* 2001b;49:606–14.
- Yeragani VK, Sobolewski E, Igel G, Johnson C, Jampala VC, Kay J, et al. Decreased heart-period variability in patients with panic disorder: a study of Holter ECG records. *Psychiatry Res* 1998;78:89–99.