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Physical activity and respiratory behavior in daily life of patients with panic disorder and healthy controls

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ABSTRACT

Panic disorder (PD) has been linked in laboratory investigations to respiratory alterations, particularly persistent respiratory variability. However, studies of PD respiratory pattern outside the laboratory are rare, have not controlled for the confounding influence of varying levels of physical activity, and have not addressed whether abnormalities in respiratory pattern vary depending on the intensity of physical activity. Cognitive and biological theories of PD, in fact, predict that respiratory alterations may be particularly pronounced when patients are physically active. This study assessed physical activity and respiratory pattern of 26 PD patients and 26 healthy controls (HC) during two waking periods of daily life (9:00–21:00) one week apart. Respiratory data were stratified for predefined levels of physical activity (inactivity, minimal movement, slow/moderate/fast walking, and running) and analyzed using linear mixed models. Groups did not generally differ in respiratory measures, although PD patients did show elevated variability of absolute levels of tidal volume during minimal movement and slow walking (root mean squared successive differences). Other ways of analyzing tidal volume variability based on relative levels, percentage of sighing, or pooled activity levels did not substantiate this finding. Amount of time spent at different activity levels did not differ between groups, which is at variance with studies linking anticipatory anxiety with motoric agitation, and PD with self-reported avoidance of exercise. In conclusion, results provided little evidence for respiratory abnormalities or central respiratory dysregulation in PD at varying levels of activity, although instability of tidal volume regulation during low activity remains a possibility. Our research approach indicates the usefulness of stratification of real life data on the basis of levels of activity, as well as how ambulatory assessment strategies, complementarily to laboratory studies, may improve understanding of biological and psychological factors contributing to development and maintenance of PD and other anxiety disorders.

1. Introduction

Theoretical assumptions (Klein, 1993, Ley, 1985) and empirical evidence (Gorman et al., 1988; Gorman et al., 1994; Schwartz et al., 1996; Hegel and Ferguson, 1997; Papp et al., 1997; Abelson et al., 2001; Martinez et al., 2001; Wilhelm et al., 2001a,b,c; Caldirola et al., 2004; Blechert et al., 2007) point to trait-like persistent respiratory abnormalities in panic disorder. However, most research on panic disorder (PD) has been performed in the laboratory where PD patients are likely to be anxious and to breathe anxiously.

The few studies that have assessed respiratory pattern in the natural environment (Martinez et al., 2001; Hoehn-Saric et al., 2004) have not adequately controlled for the influence of physical activity on respiratory measures. In a previously reported study (Pfaltz et al., 2009), we adjusted for activity by restricting analyses of ambulatory respiratory data to sedentary phases. No differences between PD patients and healthy controls were found with respect to respiratory variability or other measures of ventilatory timing or volume, suggesting that previously detected respiratory alterations (Gorman et al., 1988; Schwartz et al., 1996; Abelson et al., 2001; Wilhelm et al., 2001a,b,c; Martinez et al., 2001; Caldirola et al., 2004; Papp et al., 1997; Hegel and Ferguson, 1997) reflected exaggerated emotional reactivity to experimental contexts, rather than stable trait characteristics of PD. However, the possibility remains that PD patients during daily life may display abnormal respiratory alterations related to levels of physical activity beyond sedentary states. Such alterations might be expected for several reasons.

First, PD patients tend to worry that bodily symptoms signal harmful physical consequences. According to cognitive theories of PD (Clark, 1986), this evokes anxiety that, in turn, increases bodily symptoms. In line with this theory, PD patients report increased anxiety and somatic symptoms after physical activation in the

Abbreviations: IA, inactivity; MM, minimal movement; SW, slow walking; MW, moderate walking; FW, fast walking; RU, running; V_T, tidal volume; T_{TOT}, total time; V'_m, minute ventilation.

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laboratory (Rief and Hermanutz, 1996; Ströhle et al., 2009). Given the absence of data regarding periods of activity in our previous report (Pfaltz et al., 2009), it is conceivable that physical activity might have triggered anxiety and corresponding respiratory changes among the PD patients. Second, anticipatory anxiety and panic attacks frequently occur while patients are physically active (e.g. at shopping malls or when visiting restaurants). Anxiety-induced respiratory changes might, therefore, be primarily found during episodes of physical activity and might have been missed in our previous analysis. Third, PD patients frequently try to escape anxiety-inducing situations when symptoms of panic arise. For this reason, and due to restlessness evoked by anticipatory or acute anxiety, anxiety-induced respiratory alterations might occur more frequently during physical activity than during rest. Fourth, PD patients show heightened CO_2 sensitivity in the laboratory (Gorman et al., 1994; Papp et al., 1997). Initially increased arterial CO_2 levels during the onset of physical activity might induce an exaggerated respiratory regulation, reflected by elevated minute ventilation (V'_m; alternatively: V'_E) and tidal volume (V_T) instabilities of respiratory pattern.

This study during everyday life explored respiratory alterations by comparing respiratory data stratified for different levels of physical activity. The results we will present represent an additional analysis of data described in our previous paper (Pfaltz et al., 2009). In this study, two ambulatory 24-h recordings of breath-by-breath respiratory pattern and physical activity were made in PD patients and healthy controls (HC). Our previous analyses were restricted to phases of physical inactivity. Here, we additionally analyzed respiratory pattern during varying levels of physical activity observed in daily life.

We hypothesized that in contrast to physical inactivity phases, PD patients would show respiratory alterations during higher levels of physical activity. Specifically, based on previous laboratory findings (Gorman et al., 1988; Schwartz et al., 1996; Abelson et al., 2001; Wilhelm et al., 2001a,b; Martinez et al., 2001; Caldirola et al., 2004), we examined whether PD patients, compared to HC, would manifest heightened variability of V'_m and V_T during physical activity, as well as elevations in V'_m and V_T, and decreases in respiratory cycle total time (T_{TOT}). We also hypothesized group differences in the frequency of sighs at different physical activity levels, since heightened respiratory variability in PD has been linked to frequent sighing (Wilhelm et al., 2001a; Schwartz et al., 1996).

We also had two additional aims. First, we sought to investigate whether reactivity to the measurement system, demonstrated in the laboratory (Askanazi et al., 1980; Han et al., 1997), influences respiratory patterns in real life. In our previous analysis of the data set (Pfaltz et al., 2009), we averaged respiratory data across measurement days. However, reactivity effects might have occurred during the first 24-h recording, when participants were less familiar with the monitoring system. PD patients may have displayed particularly pronounced sensitivity and stress reactions to the novel and potentially uncontrollable situation (Abelson et al., 2007; Margraf et al., 1986), resulting in heightened physiologic arousal. Larsen et al. (1998) found higher heart rates in PD patients on the first of two consecutive laboratory measurements. Similar effects might occur regarding respiratory patterns outside the laboratory. We, therefore, expected to find differences in respiratory variables between measurement days that were more pronounced in PD patients, compared to HC. In particular, we expected elevated V_T and V'_m variability on the first, compared to the second, day, which might have reflected initially elevated respiratory dysregulation due to novelty that habituated on day 2. To assess coherence between physiologic and experiential changes, we also compared self-reported anxiety levels between days in PD patients and HC.

Our analysis approach also allowed us to examine whether the two groups spent different amounts of time at varying levels of physical activity. On the one hand, PD patients might spend a larger proportion of time during low to moderate levels of physical activity, compared to HC, due to motoric agitation brought on by anticipatory anxiety or acute panic. As demonstrated by Sakamoto et al. (2008), PD patients reporting more anxiety and panic attacks show higher daily activity levels. On the other hand, self-reported avoidance of exercise (Broocks et al., 1998) or other agoraphobic situations would suggest a decreased amount of time spent at high physical activity levels. Only one study (Clark et al., 1990) objectively assessed physical activity in daily life of PD patients in comparison to healthy controls. Clark et al. (1990) found higher mean daily activity in PD patients without phobic avoidance but not in PD patients with phobic avoidance, as compared to controls. However, they did not distinguish between different activity levels and data were collected for 1-min intervals, neglecting activity changes occurring during smaller intervals. The measurement system we used overcomes these limitations, allowing a sensitive analysis of the distribution of activity levels, in addition to respiratory behavior in daily life of PD patients.

2. Materials and methods

2.1. Participants

30 PD patients and 26 HC were recruited by means of newspaper advertisements. The study protocol was approved by the local ethics committee. Before participating, participants gave written consent. Exclusion criteria for HC were current psychiatric disorders and a history of an anxiety disorder. Four PD patients were excluded due to use of medication with strong autonomic effects or a medical history affecting the respiratory system (see Pfaltz et al., 2009, for detailed exclusion criteria). This resulted in a total sample size of 26 participants per study group. PD patients who were included took the following medications: analgesic drugs (3), benzodiazepines (4), and selective serotonin reuptake inhibitors (7). Diagnoses were assigned by means of the Diagnostic Interview for Mental Disorders (DIPS, Schneider and Margraf, 2006), which is a modified German version of the Anxiety Disorders Interview Schedule for DSM-IV–Lifetime version (ADIS-IV-L; DiNardo et al., 1994). Twenty-three of the PD patients had an additional diagnosis of agoraphobia. Other additional diagnoses in the PD group included Hypochondria (1), Posttraumatic Stress Disorder (3), Social Phobia (3), and Major Depression (4). Groups were matched for age (PD: mean = 35.5, $SD = 10.9$; HC: mean = 37.1, $SD = 9.6$, $p = .057$) and gender (PD: 84.6% female; HC: 76.9% female, $p = .43$) and did not differ regarding body mass index ($p = .31$). PD patients scored significantly higher than HC on all of the following questionnaires (p-values $<.001$): State-Trait Anxiety Inventory (Laux et al., 1981), Beck Depression Inventory (Hautzinger et al., 1994), Panic Disorder Severity Scale (Shear et al., 2001), Anxiety Sensitivity Index (Ehlers and Margraf, 1993), and Mobility Inventory (Ehlers et al., 2001). Further details regarding psychometric and demographic characteristics of the study groups can be found in Pfaltz et al. (2009). Participants were not allowed to drink alcohol 24 h before testing.

2.2. Assessment of self-reported anxiety

As described in our previous paper (Pfaltz et al., 2009), data were collected as part of a larger study during which PD patients and HC captured various attributes of psychological well being and anxiety symptoms by means of electronic diaries during one week (see Pfaltz et al., in revision). Here, only self-reported anxiety for the two physiologic measurement days will be reported for subsamples of 18 PD patients and 22 HC. For technical reasons, these data were not available for the remaining participants. Every three hours (9 am, 12 pm, 3 pm, 6 pm, and 9 pm), participants rated their anxiety on a scale from 0 (not at all) to 10 (very much). Ratings referred to the past three hours or to the time since waking up for the 9 am recording. For

the present analyses, anxiety ratings were averaged across each measurement day.

2.3. Procedure

Participants underwent the diagnostic interview and returned to the laboratory for the setup of a 24-h assessment, starting at 8:30 in the morning. Participants completed the psychometric questionnaires. Subsequently, the measurement system was explained to participants and sensors and electrodes were attached. Participants then underwent a 5 min quiet sitting baseline and walked at different paces (slow, moderate, fast) for 1 min each, with the investigator walking next to them to indicate the pace of walking. This procedure allowed distinguishing between different physical activity levels during subsequent analyses. Thereafter, participants were explained how to use the electronic diary. During the subsequent 24-h monitoring, participants pursued their everyday life and, 7 days later, returned for the second 24-h recording.

2.4. Physiologic data collection

A respiratory inductive plethysmography device (LifeShirt system, VivoMetrics, Inc., Ventura, CA, USA; see Wilhelm et al., 2003a,b; Grossman, 2004; Wilhelm et al., 2006) was used to record respiratory waveforms at 50 Hz from thoracic and abdominal bands. Intensity and direction of acceleration in all three spatial axes were sampled at 10 Hz by an accelerometer placed at the level of the sternum. After the 24-h recordings, data were transferred to a personal computer and respiratory and physical activity parameters were computed by means of the Vivologic® software (VivoMetrics, Inc., Ventura, CA, USA).

During offline-analysis, gains of the two respiratory bands were proportioned by applying qualitative diagnostic calibration (QDC; Sackner et al., 1989) to the 5-min quiet sitting period. Respiratory waveforms were summed up and converted to V_T in ml, based on a calibration procedure conducted at setup of the measurements. During this procedure, participants rebreathed eight times into a plastic bag (750 ml) while sitting. Next to V_T, V'_m, and T_{TOT} (total breath time = 60/frequency of breathing per min [f]) were calculated breath-by-breath. Sigh% (total number of sighs/total number of breaths) served as measure of sigh frequency, with sighs being defined as inspiratory breath volumes greater than 2.5 times the median of a 2 min V_T moving average baseline. Root mean square of successive differences (RMSSD) of V_T and V'_m served as measures of respiratory variability.

Accelerometer data channels (three orthogonal axes) were low-pass filtered, rectified, smoothed, and averaged across channels, resulting in the AccM motion indicator, which reflects the intensity of physical activity.

2.5. Data assignment to physical activity categories

We used the above described quiet sitting and paced walking procedures to establish different physical activity categories in a subsample of 15 PD patients and 15 HC. Using customized programs (Wilhelm and Peyk, 2005), AccM was averaged across the quiet sitting and the slow, moderate, and fast walking calibration intervals. By averaging AccM of the quiet sitting and slow walking categories, we obtained an additional, minimal movement category, which was considered to be relevant to daily life. A sixth (running) category was calculated by summing up the mean "fast walking" AccM with the mean AccM difference between all activity categories. To obtain upper and lower limits of the activity categories, AccM means of each category and its adjacent two categories were calculated. This way, the following six categories and corresponding AccM boundaries were established: Inactivity (values ≥ 0 and <1.14), minimal movement (values ≥ 1.14 and <2.69), slow walking (values ≥ 2.69 and <4.20), moderate walking (values ≥ 4.20 and <5.65), fast walking (values ≥ 5.65 and <7.10), running (values ≥ 7.10). Using these boundaries, each breath was assigned to one of the six categories by searching through the AccM signal, which was smoothed with an 8 s moving average window to enhance stability of the signal. For each respiratory variable, average values for time segments of the same activity category were computed across the waking day, i.e., from 9 am to 9 pm.

2.6. Statistical analysis

Data were analyzed using SPSS 16.0 (SPSS Inc, Chicago, Illinois). Respiratory variables and the percentages participants spent within the different activity levels were assessed for normality of distribution and, if necessary, transformed before analyses. Regarding T_{TOT} and Sigh%, values exceeding three standard deviations from the mean of the total study group were considered as outliers and were thus excluded from the analyses. Regarding the respiratory volumetric variables, values for all of the variables were excluded for one of the patients, due to incorrect application of the calibration procedure. Thereafter, if V_T values exceeded three standard deviations from mean V_T of the total study group, these values, as well as the corresponding V'_m, RMSSD of V_T, and RMSSD of V'_m values were excluded from the analyses. For HC, this resulted in the following percentages of values excluded: T_{TOT} and Sigh%: 0%, V'_m, V_T, RMSSD of V'_m, and RMSSD of V_T: 4.6%. In patients, the following percentages were excluded: T_{TOT}: 0.3%, Sigh%: 1.6%, V'_m, V_T, RMSSD of V'_m, and RMSSD of V_T: 5.2%. Percentages of excluded values did not differ significantly between groups for any of the respiratory variables (p-values > .053).

For each respiratory variable, a primary analysis was carried out by computing a linear mixed model (Pinheiro and Bates, 2000) with Measurement Day (day 1, day 2) and Activity Level (inactivity, minimal movement, slow walking, moderate walking, fast walking, and running) as within-subjects variables and Group (PD, HC) as between-subjects variable. An unstructured variance–covariance matrix was used to model residual dependencies as preliminary analysis had shown that variances strongly increased with increasing activity level and correlations among different activity levels varied considerably without showing any pattern.

Regarding respiratory variables, we calculated two additional, secondary analyses. First, V_T changes across time as measured by the LifeShirt system have been demonstrated to reliably reflect V_T and V'_m changes measured with spirometry (Grossman et al., 2010). However, this recent paper indicates that although the calibration procedure we conducted at setup of the measurements does not provide completely accurate absolute values for volumetric measures, the accuracy for within-subject relative changes is very good. Therefore, for the volumetric variables V_T and V'_m, as well as for RMSSD of V_T and V'_m, we additionally conducted the mixed model analyses by calculating relative changes from physical inactivity to minimal movement, slow walking, moderate walking, fast walking, and running, expressed in percentages. Second, given the non-invasiveness of the measurement system we used, reactivity effects might habituate relatively fast and could thus be obscured by including respiratory data of the complete measurement days. To assess this possibility, an additional linear mixed model with Measurement Day and Activity Level as within-subjects variables and Group (PD, HC) as between-subjects variable was conducted for each respiratory variable. In these analyses, only data of the first three hours were included per measurement day.

To assess changes in self-reported anxiety between measurement days as well as potential group differences regarding these changes, a 2 × 2 repeated measures ANOVA was calculated with Group (PD, HC) as one factor and Day (day 1, day 2) as repeated measurement factor.

To assess potential group differences in the amount of time spent at different physical activity levels on the two measurement days, a

Table 1
Results for the Group, Activity Level and Day main effects and for the Activity Level × Group, Group × Day, and Activity Level × Day interactions of the primary mixed model analyses performed for the respiratory variables.

	Group		Activity Level		Day		Activity Level × Group		Group × Day		Activity Level × Day	
	F(*df*)	*p*	*F*(*df*)	*p*	*F*(*df*)	*p*	*F*(*df*)	*p*	*F*(*df*)	*p*	*F*(*df*)	*p*
RMSSD V_T	1.7 (1,91)	.197	384.4 (5,90)	.000	0.0 (1,91)	.971	2.5 (5,90)	.039	0.0 (1,91)	.990	0.2 (5,90)	.953
RMSSD V'_m	3.5 (1,91)	.064	504.2 (5,90)	.000	0.0 (1,91)	.829	0.4 (5,90)	.880	0.0 (1,91)	.866	1.2 (5,90)	.325
V'_m	3.7 (1,91)	.059	400 (5,90)	.000	0.0 (1,91)	.889	1.8 (5,90)	.131	0.0 (1,91)	.843	0.4 (5,90)	.868
V_T	2.3 (1,91)	.136	176.8 (5,90)	.000	0.0 (1,91)	.942	2.1 (5,90)	.075	0.0 (1,91)	.879	0.4 (5,90)	.848
T_{TOT}	0.4 (1,96)	.511	100 (5,96)	.000	0.0 (1,96)	.933	1.1 (5,96)	.378	0.0 (1,96)	.909	0.6 (5,96)	.618
Sigh%	0.1 (1,86)	.765	6.4 (5,86)	.000	0.4 (1,86)	.530	0.6 (5,86)	.724	0.1 (1,86)	.705	0.6 (5,86)	.665

Abbreviations: V_T, tidal volume; V'_m, minute Ventilation; T_{TOT}, total breath time; Sigh%, total number of sighs/total number of breaths.

2 × 2 × 6 repeated measures analysis of variance (ANOVA) was calculated with Group (PD, HC) as one factor and Measurement Day (day 1, day 2) and Activity Level (inactivity, minimal movement, slow walking, moderate walking, fast walking, running) as repeated measurement factors. ANOVA results were corrected for violations of the sphericity assumption and ε reported where appropriate. Effect size values η^2 were computed. Alpha was set to .05 for all statistical analyses.

3. Results

3.1. Self-reported anxiety

In PD, mean anxiety levels were 2.3 ($SD = 0.8$) on day one and 2.2 ($SD = 0.4$) on day two. In HC, mean anxiety levels were 0.3 ($SD = 1.5$) on day one and 0.1 ($SD = 2.4$) on day two. Overall, anxiety levels were significantly higher in PD patients compared to HC ($F(1,38) = 27.7$, $p < .001$) but no Day ($p = .623$) main effect and no Day × Group interaction ($p = .855$) were found.

3.2. Respiratory variables

Regarding the primary analyses, no significant Activity Level × Day × Group interactions (p-values >.12) were found for any of the respiratory variables. Table 1 shows the results of the remaining interactions and main effects assessed by the primary mixed model analyses.

Group main effects did not reach significance for any of the respiratory variables. All variables varied highly significantly across the different activity levels (see Fig. 1). However, no significant Activity Level × Day interactions were found. Also there were no significant Day main effects and Group × Day interactions. RMSSD of V_T was the only variable for which a Group × Activity interaction was found. This interaction reflects somewhat stronger increases in V_T variability during minimal movement ($p = .054$) and slow walking ($p = .06$) but not during moderate walking ($p = .17$), fast walking ($p = .59$), and running ($p = .46$) in PD patients compared to HC.[1]

Results of the secondary mixed model analyses assessing *relative* changes of activity periods compared to the inactivity period (in %) in V_T, V'_m, RMSSD of V_T, and RMSSD of V'_m were comparable to the results based on absolute values for these variables, with one exception: the Group × Activity interaction for RMSSD of V_T did no longer reach significance ($p = .25$). Activity main effects remained highly significant (p-values <.002) whereas the Group and Day main effects did not reach significance (p-values >.20). Neither the Group × Day × Activity interaction nor any of the two-way interactions reached significance (p-values >.12).

When including only respiratory data of the first three hours per measurement day, we again found no significant Group × Day × Activity, Group × Activity, or Group × Day interaction (p-values >.075). Respiratory variables still varied significantly across the different activity levels (p-values <.007), and Group and Day main effects did not reach significance (p-values >.089). Significant Day × Activity interactions were found for RMSSD of V'_m ($p = .045$), V_T ($p = .035$), and Sigh% ($p = .033$), reflecting somewhat higher values for both groups in these variables on day two compared to day one during minimal movement, slow, moderate, fast walking, and running but not during inactivity. Follow-up pairwise comparisons between days carried out separately for the different activity levels did however not reach significance (p-values >.061), except for RMSSD of V'_m, which, during fast walking but not during the remaining activity levels, was significantly higher on the second compared to the first measurement day ($p = .048$).

3.3. Distribution of physical activity levels

Table 2 shows the average percentages of time spent in each activity level (and thus the percentage of data included in the analyses of respiratory data for each activity level) in PD patients and HC, separately for each day of measurement. Overall, groups did not differ regarding the percentage of data included ($p = 0.5$, $\eta^2 = .01$) but the percentage of data included was higher for lower physical activity categories, as indicated by a significant main effect for Activity Level ($F(5,250) = 1279.4$, $p < .001$, $\varepsilon = .308$; $\eta^2 = .96$). The distribution of data across different activity levels was unaffected by Group ($p = .17$, $\eta^2 = .04$) and Day ($p = .32$, $\eta^2 = .02$). No main effect for Day and no Group × Day interactions were found (p-values >.37, η^2-values <.02), indicating that overall, neither group specific nor group non-specific changes in the percentage of data included occurred between measurement days. This pattern was not affected by activity levels, as reflected by a non-significant Activity Level × Day × Group interaction ($p = .69$; $\eta^2 = .01$).

4. Discussion

This is the first time respiratory pattern has been assessed at different physical activity levels in the natural environment of PD patients. Our previous analysis (Pfaltz et al., 2009) was restricted to sedentary periods in an attempt to closely mimic laboratory baseline conditions. In contrast to frequently observed laboratory baseline findings of respiratory abnormalities in PD, particularly regarding exaggerated V_T variability, in that analysis, we found no evidence for such abnormalities during the daily life of patients. In our expanded analysis, presented here, that includes not only sedentary periods but

[1] Statistical power of the mixed model analyses may have been limited by the fact that a rather high number of six activity categories were included. Therefore, in exploratory analyses, we collapsed activity categories further to two categories ('inactivity to slow walking' and 'moderate walking to running'). With two exceptions, results were highly comparable to the findings of the primary analyses: 1) The Activity Level main effect for Sigh% was no longer significant ($p = .331$); and 2) The Group × Activity interaction for RMSSD of V_T was no longer significant ($p = .470$).

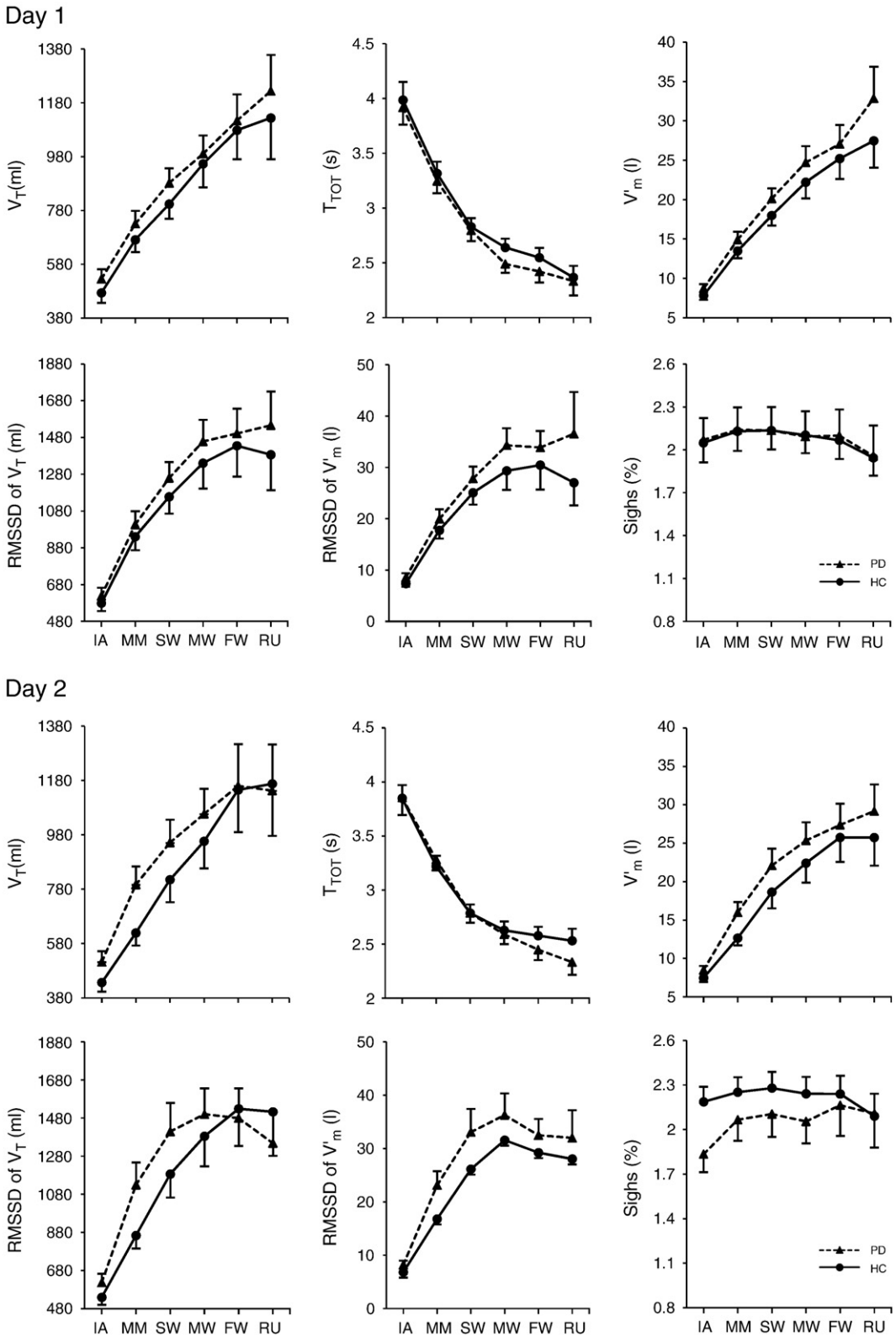

Fig. 1. Means (SE) of respiratory variables in panic disorder (PD) patients and healthy controls (HC) across different activity levels on the first (upper panel) and second (lower panel) measurement day. Abbreviations: IA, inactivity; MM, minimal movement; SW, slow walking; MW, moderate walking; FW, fast walking; RU, running; V_T, tidal volume; T_{TOT}, total time; V'_m, minute ventilation.

the full range of activity levels occurring in awake daily life, the earlier results were largely confirmed. However, we now find tentative evidence for group differences in V_T variability that are restricted to phases of relatively low, but not completely sedentary, physical activity.

4.1. Respiratory changes across activity levels

Respiratory variables varied significantly across activity levels, confirming the sensitivity of our method to detect activity-associated and thus largely metabolically determined respiratory changes.

Table 2
Mean (SD) percentages of time spent at each activity level on day one and day two in PD patients and HC.

	Inactivity		Minimal Movement		Slow Walking		Moderate Walking		Fast Walking		Running	
	PD	HC	PD	HC	PD	HC	PD	HC	PD	HC	PD	HC
Day 1	65.6 (18.0)	62.2 (19.1)	18.7 (10.5)	19.4 (9.5)	8.3 (4.8)	9.2 (5.6)	3.9 (2.9)	4.5 (3.9)	2.1 (2.6)	2.6 (3.4)	1.0 (2.1)	1.7 (3.1)
Day 2	65.1 (19.4)	60.9 (18.5)	19.1 (11.8)	20.1 (10.0)	7.8 (4.7)	9.6 (5.6)	3.8 (2.8)	4.2 (2.9)	2.6 (3.6)	2.4 (2.8)	1.0 (1.8)	2.4 (3.4)

Regarding group differences in the pattern of respiratory changes across activity levels, PD patients showed stronger increases in V_T variability during minimal movement and slow walking compared to HC, although follow-up comparisons between groups only reached marginal significance. On the one hand, the absence of significant follow-up comparisons might be related to the fact that our sample sizes were rather small. On the other hand, secondary analyses based on relative changes of respiratory volumetric measures were not significant, although relative changes have recently been shown to be much more accurate than absolute changes when V_T estimates are derived from inductive plethysmography (Grossman et al., 2010) and variability measures of absolute V_T are strongly related to V_T magnitude. Also, when collapsing respiratory data across two activity levels to increase statistical power, or when examining only sedentary periods (Pfaltz et al., 2009), no abnormalities in V_T variability or other respiratory variables could be detected, at odds with the hypothesis that PD patients display aberrant or exaggerated respiratory activity, and abnormal ventilatory control, during most of awake daily life. The trend for PD patients to show higher V_T variability during minimal movement and slow walking may, nevertheless, be noteworthy since this is the first time that elevated V_T breath-by-breath variability has been demonstrated in PD patients outside the laboratory.

Additionally, we did not detect group differences in frequent sighing, previously related to breathing irregularities in the laboratory (Schwartz et al., 1996). Rather, the Sigh% variable showed a different pattern of change across activity levels than RMSSD of V_T, whereas in the laboratory, sighs and V_T variability are often strongly related (e.g., Abelson et al., 2001). In the ambulatory context, RMSSD of V_T might thus reflect movement to a stronger degree than Sigh%. This may be an effect of the running baseline adjustment of the sigh threshold, which will increase in parallel with mean V_T values during increasing physical activity levels. On the other hand, RMSSD of V_T is affected to a large degree by elevated V_T at higher activity levels. Interestingly, the elevated V_T variability during low levels of physical activity in PD was not paralleled by elevated V'_m variability ($p<.90$).

The fact that PD patients may possibly show elevated V_T variability during low but not during moderate or high levels of physical activity also points out how methodologically challenging it may be to demonstrate emotionally coupled respiratory changes during heightened levels of activity, since ventilation becomes increasingly under metabolic control (Forster and Pan, 1988) and thus is likely to be less influenced by emotional factors than during states of quiescence. In future studies, it might be reasonable to mainly focus on potential group differences in respiratory pattern during lower levels of physical activity, since more subtle, emotionally coupled respiratory changes might be difficult to detect at higher levels of activity.

In terms of cognitive theories of PD and laboratory findings (Clark, 1986; Rief and Hermanutz, 1996; Ströhle et al., 2009), one may expect respiratory abnormalities to be associated with physical activity, particularly in PD patients because of their fear of bodily symptoms being reflected in respiratory hyperactivity. This effect should increase with increasing activity levels. Our findings do not support this contention. In treatment contexts, in particular during confrontation exercises directed at inducing physiologic changes (e.g. running up the stairs), many patients do not report anxiety, since they correctly attribute these changes to the pursued activity. We cannot evaluate whether similar processes in our study could explain the absence of clear, activity-related atypical respiratory alterations in PD because the type of daily activities and participants' causal attributions and potentially catastrophic interpretations of associated physiologic changes were not assessed. In future studies, it will be important to capture daily activities and associated cognitive and emotional processes.

PD patients are highly sensitive towards novel situations (Abelson et al., 2007). The environment of laboratory investigations is often characterized by unknown people, apparatuses, and prescribed procedures, possibly inducing respiratory alterations that are not necessarily characteristic of daily life (Wilhelm and Grossman, 2010). The relative lack of atypical respiratory alterations among PD patients (except for the tentative effect for atypical V_T variability at low activity levels) may thus also reflect the absence of novel or uncontrollable situations during our recordings, since patients are likely to be familiar with most daily activities or can avoid engaging in novel situations in daily life. In this regard, it might be interesting to examine if different results are obtained in PD patients without agoraphobia. Twenty-three of our 26 PD patients had agoraphobia and thus probably avoided anxiety-inducing situations, minimizing anticipatory or acute anxiety and associated respiratory changes. Still the heightened level of state anxiety among PD patients, in the absence of substantial respiratory abnormalities does not speak to the likelihood that respiratory function was related to degree of anxiety or that anxiety is causally linked to central respiratory control mechanisms.

4.2. Reactivity effects

When examining respiratory data of the complete measurement days (from 9 am to 9 pm), neither study group showed elevated V_T or V'_m variability on the first compared to the second measurement day. Also, no differences were found for other variables between days. However, when inspecting only the first three hours of each day, both groups unexpectedly showed elevated, rather than diminished V_T, Sigh%, and V'_m variability on the second, compared to the first, measurement day during all activity levels, except during inactivity. Nevertheless, in follow-up comparisons, this difference between days only reached significance for V'_m variability during fast walking. Regarding experiential changes, PD patients showed elevated levels of anxiety compared to HC on both days, likely reflecting anticipatory anxiety and fear of agoraphobic situations in these patients. Yet, as opposed to respiratory variables for the first three hours, neither patients nor HC showed differentially elevated anxiety levels between recording days.

Therefore, when assessing respiration across extended periods, respiratory patterns seem unlikely to be influenced by reactivity effects to the measurement system. However, during the first few hours of recording, reactivity effects in certain respiratory variables might occur while participants are physically active. These findings remain preliminary and need to be confirmed by other studies to ensure that significant results are not a result of alpha error inflation due to multiple testing.

Consequently, neither PD patients nor healthy controls seem to be particularly sensitive to measurement instrumentation during daily life—at least when employing a non-invasive measurement system like the one we used. This supports the use of comfortable, user-

friendly ambulatory recording systems to minimize reactivity to measurement when assessment of respiratory patterns is attempted among study groups like PD patients who are highly sensitive towards novel situations (Abelson et al., 2007).

4.3. Distribution of physical activity levels

We were able to establish ecologically reasonable categories of physical activity, related to respiratory pattern, that could be used to assess different research questions outside the laboratory. Our analysis revealed no distinct activity pattern in PD patients compared to healthy controls. This may be surprising, since PD has been associated with motoric agitation due to anticipatory anxiety, as well as self-reported avoidance of exercise (Broocks et al., 1998). Consequently, one might have predicted group differences both in low (more activity in PD) and high (less activity in PD) levels of physical activity. Nevertheless, our fine-grained results, based on a novel categorization of physical activity levels in daily life (see Grossman et al., 2004, for a different approach based on within-individual quintiles of physical activity), are in accordance with previous research that showed no differences in daily activity between controls and PD patients with agoraphobic avoidance (Clark et al., 1990). The latter group did find, compared to controls, elevated daily activity in PD patients without agoraphobic avoidance. In our PD sample, only 3 out of 26 PD patients did not have an additional diagnosis of agoraphobia. We were, therefore, unable to explore differences in the distribution of activity levels between controls and PD patients without agoraphobic avoidance, although this would be a worthwhile pursuit in the future.

4.4. Limitations and conclusions

This study has several limitations. First, sample sizes were rather small, and future investigations with larger samples would be desirable. Second, the calibration procedure we used has recently been shown not to produce completely accurate absolute V_T or V'_m estimation under ambulatory conditions when compared to direct gold standard volumetric measurement (Grossman et al., 2010). Although relative changes in these parameters, which we also assessed, do seem to be accurately characterized by our method (see Grossman et al., 2010), future ambulatory studies, employing more accurate assessment of volumetric parameters, are needed in PD research.

Third, we did not assess participants' habitual physical exercise levels. According to self-reports, PD patients avoid exercise (Broocks et al., 1998), which points to reduced physical fitness in PD patients and may influence respiratory patterns. Fourth, we did not perform an analysis of speech activity in daily life and how it is associated with respiration. On- and offsets of speaking, as they occur during social interaction, would clearly induce respiratory variability, and speaking per se has been associated with respiratory changes, including breath-by-breath variability in various respiratory parameters (Wilhelm et al., 2003a,b). Thus, group differences in speech activity may have concealed group differences in respiratory pattern or, on the other hand, may have been responsible for the group differences in V_T variability that was found. For example, agoraphobic PD patients might have stayed home during recordings to avoid feared situations, resulting in reduced social interactions and associated speech activity. This may have masked subtle group differences.

Finally, some of the PD patients took SSRIs or benzodiazepines. SSRIs may be associated with subtle autonomic side effects but seem to have no or only minor impact on respiratory pattern (Siepmann et al., 2003). Benzodiazepines do not seem to affect V'_m, end-tidal pCO_2 or oxygen consumption, but their use is associated with elevated respiratory variability during the laboratory baseline assessment and has been attributed to frequent wake–sleep changes due to drowsiness (Carraro et al., 2009). Thus, an influence of SSRIs seems unlikely, while benzodiazepine use would have biased results on respiratory variability and worked toward finding elevated respiratory variability in PD, albeit only during relatively sedentary states and not during physical activity periods.

Despite these limitations, the present analysis provides important initial insights to the question of whether PD patients show abnormal respiratory pattern across different activity levels. Consistent with our previous analyses during periods of physical inactivity (Pfaltz et al., 2009), atypical respiratory activity was generally not seen in PD during more active states. Nevertheless, the present analyses do provide possible evidence for group differences in V_T variability during two low levels of physical activity that comprise about 27% of awake daily functioning. Because these group differences could not be confirmed by secondary analyses based on relative changes of respiratory measures, were not accompanied by differences in V'_m variability and disappeared when analyses compared two collapsed levels of activity, it seems premature to draw firm conclusions regarding this finding.

This specific result is, nevertheless, partially in line with previous results of heightened respiratory variability (Gorman et al., 1988; Schwartz et al., 1996; Abelson et al., 2001; Wilhelm et al., 2001a,b; Martinez et al., 2001; Caldirola et al., 2004), as well as with biological theories on PD, emphasizing the role of abnormal respiratory pattern in the etiology of PD (e.g., Klein, 1993), although these reports are commonly based upon ventilation measured during sedentary state and not during low levels of physical activity. Given the important theoretical and therapeutic implications of enhanced understanding of factors contributing to the development of PD, it seems essential to further explore possible respiratory abnormalities in patients with PD in relation to variations in activities of daily life. Complementary approaches involving both ambulatory assessment and laboratory studies may serve to provide a more complete picture of the psychological and physiological factors relevant to the etiology and maintenance of PD (see Wilhelm and Grossman, 2010).

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