Published in final edited form as:

J Psychiatr Res. 2010 December ; 44(16): 1137–1147. doi:10.1016/j.jpsychires.2010.04.012.

Twenty-four hour Skin Conductance in Panic Disorder

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Abstract

Skin conductance, physical activity, ambient temperature, and mood were recorded for 24 hours in 22 panic disorder (PD) patients and 29 healthy controls. During the day, subjects performed standardized relaxation tests (ARTs). We hypothesized that tonically elevated anticipatory anxiety in PD during waking and sleeping would appear as elevated skin conductance level (SCL) and greater skin conductance (SC) variability. Mean SCL was higher during both usual waking activities and sleeping in PD, but not during the ARTs. Group SC variability differences did not reach significance, perhaps because of variance unrelated to anxiety. Analyses indicated that in the PD group, antidepressant medication reduced mean SCL whereas state anxiety had the opposite effect during the day. Depressive symptoms reported during the day were related to elevated mean SCL on the night of the recording. The rate and extent of SCL deactivation over the night was equal in the two groups. However, PD patients had more frequent interruptions of deactivation that could have arisen from conditioned arousal in response to threat cues during sleep.

Descriptors

Panic Disorder; Anxiety; Skin Conductance; Ambulatory Monitoring; Sleep

Anxiety in panic disorder (PD) is not confined to panic attacks but is present at a lower intensity before and after attacks. This kind of anxiety in PD is often called anticipatory because theoretically it results from exteroceptive and interoceptive conditioning to threat cues associated with panic attacks (Bouton et al., 2001). With interoceptive conditioning, bodily sensations experienced during panic attacks become conditioned stimuli, eliciting anxiety that later may eventuate in panic. External cues become conditioned stimuli for anxious avoidance of places and situations. Catastrophic interpretations of bodily sensations may be a cognitive aspect of this conditioning (Clark, 1986).

It is unclear, however, whether anticipatory anxiety would also lead to sustained physiological activation in PD patients. One way to elicit physiological expressions of anticipatory anxiety is to threaten healthy humans with electric shock – a stimulus that is aversive as a panic attack is to a PD patient. Increases in skin conductance level (SCL) and in the number of nonspecific fluctuations are observed in these subjects as part of a pattern of an emotional activation (e.g., Gaebelein et al., 1974; Lanzetta et al., 1976; Monat et al., 1972). The activation is expressed in multiple physiological systems including the brain, where blood flow increases in the left insula, right temporal sulcus, left fusiform gyrus, and left anterior cingulate cortex (Chua et al., 1999). Electrodermal measures may express this

activation better than cardiovascular ones. Fowles (2000) has argued that increased electrodermal activity specifically reflects anxiety anticipating future threat such as would be the next panic attack, while heart rate reflects fear of current threat (for a discussion, see Parente et al., 2005). Indeed, skin conductance measures have been elevated in PD patients when cardiovascular ones were normal (Braune et al., 1994; Hoehn et al., 1997; Parente et al., 2005).

Consistent with these theoretical expectations, many studies have reported greater skin conductance activation in PD patients than in comparison groups under diverse conditions, ranging from resting baselines to watching a panic attack video (see table 1). The findings, however, are far from consistent. In the one ambulatory study where SC was recorded during daily activities, SCL was not higher in PD patients than in non-anxious controls, either during non-anxious periods or periods of stress and panic (Hoehn-Saric et al., 2004). Instead these authors found lower skin conductance variability (mean squared successive differences in SC, MSSD) values in PD patients, which led them to assert that PD is characterized by “diminished autonomic flexibility.” Reported laboratory studies (see Table 1) vary methodologically in several ways that might contribute to their inconsistency: (a) PD was diagnosed using different versions of the DSM. (b) PD severity varied. (c) Agoraphobic fears were not always assessed. Such fears are especially likely to affect the results of testing in small rooms or chambers, if the subject is alone, and if tethered with electrode leads or tubes to stationary equipment (Roth et al., 1986). (d) Variations in depression could have been important since depression can lower electrodermal activity (Argyle, 1991; Ward et al., 1983). (e) Psychoactive medication or any medication with autonomic effects could have influenced outcomes. For example, it is noteworthy that the two studies that allowed the use of benzodiazepines did not show significant differences in SCL or the number of NSF's (Argyle, 1991; Birket-Smith et al., 1993). The ambulatory study of Hoehn-Saric and colleagues (2004) prohibited medications affecting the central or autonomic nervous system, but did not assess possible effects of agoraphobia or depression on their electrodermal measures.

Thus, although theoretical considerations and experimental evidence give us reason to believe that PD patients would exhibit elevated SCL and a higher rate of NSF's during normal daytime activities, data supporting this hypothesis are inconsistent and come exclusively from laboratory environments where anxiety levels may be more a reaction to an artificial, restrictive setting than representative of a PD patient's daily reality. The one ambulatory study failed to find elevated SCL or higher rates of NSF's in PD. In fact, a measure of fluctuations (MSSD) was lower. That study, however, was limited to daytime recording of 6 out of every 30 minutes for a total of 6 hours.

PD patients might be expected to have abnormal electrodermal activation during sleep for at least two reasons. First, panic attacks in PD are not confined to the day but also occur at night. Epidemiological data on nocturnal panic attacks is limited, but it is estimated that between 44% and 71% of PD patients have experienced a nocturnal panic attack at least once (Craske & Tsao, 2005). Craske and colleagues (Craske & Tsao, 2005; Craske & Waters, 2005) propose that nocturnal panic attacks are conditioned responses to perceived changes in physiological state during sleep. Even though asleep, PD patients may process threat cues and react with elevations in anxious arousal that can escalate to panic. Second, PD is frequently comorbid with depression, which is strongly associated with sleep disturbances (for a summary of these disturbances, see Benca, 2005). PD patients have more sleep complaints than controls, even in the absence of either reported nocturnal panic attacks or comorbid depression (Overbeek et al., 2005), although polysomnographically measured sleep parameters are usually normal (e.g., Arriaga et al., 1996; Landry et al., 2002; Stein et al., 1993b). In one study, measures of heart rate variability were lower in PD patients during

sleep (McCraty et al., 2001), which is consistent with less parasympathetic and more sympathetic activation, although heart rates did not differ. Heart rate and blood pressure are not elevated in PD during sleep (Abramson et al., 1989; Clark et al., 1990) unless patients have comorbid major depression (Abramson et al., 1989). As far as the authors know, skin conductance has never been reported for PD patients during sleep.

The study here is unique in measuring skin conductance, temperature, and activity ambulatorily for a 24 hour period in PD patients and matched non-anxious controls. We had three *a priori* hypotheses: First, that during waking periods, skin conductance levels (SCL) and measures of non-specific skin conductance fluctuations (rate of non-specific fluctuations, 1-min SC standard deviation, and mean square successive difference) would be higher in the panic patients than in non-anxious controls. In spite of mixed empirical findings, it is compelling theoretically that PD patients would be more sympathetically activated by anxiety from cues that had previously caused attacks or from attacks themselves. Second, that during waking periods, PD patients would be less able to relax than controls when told to sit quietly and relax and that this would manifest itself in less negative SCL slopes, higher SCL and more non-specific skin conductance fluctuations (both rate of non-specific fluctuations and 1-min SC standard deviation) during our Ambulatory Relaxation Test (ART). Slower deactivation would be consistent with findings from studies reviewed above (Table 1) using a similar procedure in the laboratory. Third, that the differences postulated for waking would also be present in some form during sleeping periods since PD patients often complain of poor sleep. For the same reason, night-time physical activity should be higher in PD patients than controls. For hypotheses that were confirmed, we planned exploratory analyses of possible relationships between skin conductance and state anxiety, panic attacks, agoraphobic symptoms, state depression, and subjective sleep disturbance. Furthermore, we planned to explore an alternate index of skin conductance activation, namely run lengths of ascending or descending SC activation.

Methods

Participants

Participants from the local community were recruited by advertisement for studies of the effectiveness of breathing training for anxiety disorders. Twenty-two panic disorder (PD) patients (42.7 ± 15.0 yrs, 64% women) were matched with 29 healthy controls (42.1 ± 12.3 yrs, 66% women) on age, gender, race, and body mass index (BMI). Patients met DSM-IV criteria for PD with or without agoraphobia, with panic attacks of frequency and severity that were at least mild on the Panic Disorder Severity Scale (PDSS - Shear et al., 1997). They were willing to undergo a 5-session course of breathing training and to accept the possibility of an 8-week treatment delay if assigned to the waiting list group. The outcome of that study will be reported elsewhere. Healthy controls were selected not to have a current diagnosis or history of any anxiety disorder.

Exclusion criteria for all participants were a history of, or current, psychosis, cognitive impairment (e.g., a prior diagnosis of dementia, brain damage, or mental retardation or clear evidence of impaired memory or understanding during interactions with the interviewers), or substance abuse or dependence in the past year. They were allowed to continue on stable doses of medicines prescribed by physicians, but were excluded if they were taking drugs with substantial anticholinergic effects, such as tricyclic antidepressants, which have direct effects on skin conductance. They were also told not to take benzodiazepines prescribed "as needed" on the day of testing. However, no blood tests were performed on the day of testing to confirm adherence.

Procedure

This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed and approved by the Stanford Institutional Review Board. Individuals who passed the phone screening were invited to an appointment where they gave written informed consent for further assessment after the nature of the procedures had been fully explained. The assessment began with a Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2001). If no grounds for exclusion were found, they were asked to wash their hands with soap in preparation for the application of skin conductance electrodes (Dawson et al., 1990; Venables & Christie, 1980). Next they underwent testing in a laboratory room where numerous autonomic and respiratory measures were recorded while they were trying to relax and to change their breathing according to several different instructions. The results of this testing have been reported elsewhere (Conrad et al., 2007; Roth et al., 2008; Wollburg et al., 2008).

After the laboratory session, the ambulatory monitoring device was connected. Participants wore it continuously until they returned the next day. Recording usually started and ended at around 14:00 with the length of recording ranging between 18:40 and 25:50 with a mean of 23:40 (h:min). During that time, participants performed four identical ambulatory relaxation tests (ARTs). For each test they first walked at a normal pace for 3 min to establish comparable baseline activation levels in each participant during a standard, non-stressful activity. They then sat quietly without talking or moving for 8 min, during which they were instructed to relax. Test instructions and timing had been recorded on a portable cassette recorder, which subjects played at the prescribed times of each test (see Table 2): the first in the hospital at a mean time of 14:25 hours, the second in the afternoon after leaving the hospital (mean 18:40), the third the next morning (mean 9:40) before returning to the hospital, and the fourth back at the hospital (mean 13:25). In the hospital, the quiet sitting took place in a spacious room without the experimenter present; outside the hospital subjects were to find a quiet, undisturbed place to sit. Subjects filled out a short questionnaire each time before and after they completed the 8 min relaxation part of the ART, and also at 16:00 and 20:00 the first day, as well as 8:00 the second day. This questionnaire assessed their current emotional state and their emotional state during the last min of relaxation (e.g., “anxious”, “worried”), respectively on a subjective units of distress scale from 0, “not at all”, to 10, “extremely”. Of most interest for this report is the adjective “anxious”. Furthermore, participants were asked to report the number of panic attacks during the day, as well as during the night. On the morning of the second day of recording, subjects reported the number of awakenings during sleep, subjective sleep duration, and whether they felt rested after sleep.

In addition, participants were given a packet of questionnaires on the first day, which they returned completed the next day. These included the Beck Anxiety Inventory (Beck et al., 1988) to be answered for the past week (internal consistency, $\alpha = .92$), the Mobility Inventory for Agoraphobia (Chambless et al., 1985) with no time frame given ($\alpha = .91-.97$), and the Pittsburgh Sleep Quality Index (Buysse et al., 1989) to be answered for the past month ($\alpha = .83$). The Beck Depression Inventory (Beck et al., 1961) to be answered for the past week ($\alpha = .86$), was also given to all participants except for 8 controls who received the short version of the Beck Depression Inventory ($\alpha = .91$, Abdel-Khalek, 2001).

Physiological Assessment

Physiological data were recorded with a 3-channel ambulatory digital recorder (3991×/3 BioLog, UFI, Moro Bay, CA, USA) worn in a handbag or waist pack. The device measures 3.3 × 7.1 × 12.7 cm and weighs 230 g with its battery. Channels were (1) skin conductance measured by applying 0.5 V DC to electrodes on the middle or lower phalanges of the index

and middle finger of the non-dominant hand. Skin conductance in the range 0.01–39.95 μS (iemens) was sampled with $\pm 0.01 \mu\text{S}$ resolution at 10 Hz and digitally low-pass filtered at 0.5 Hz. Disposable electrodes with a circular contact area of 1 cm diameter pre-filled with isotonic gel were used (EL507, Biopac Systems, Inc., Goleta, CA, USA). In order to maintain contact for 24 hours, additional Biopac isotonic gel (Gel 101) was applied to the center of the electrode. (2) Bodily activity was sampled at 1 Hz from a UFI 1110 Jitterbug Actigraph accelerometer attached to the participant's ankle on the same side as the non-dominant hand. This device responds to motion in all directions and axes with oscillations around 0 V. (3) Ambient temperature was sampled with an accuracy of 0.1 degrees C at 0.1 Hz from a sensor in the pack. The recorder had an event-marker button, with which participants could indicate the beginning of the ART, periods of emotional arousal, time of getting into bed and turning out the lights, getting up in the morning, or unusual events. The nature of the event was recorded in a paper log along with the time the button was pressed. Bodily activity and temperature were measured to account for their possible influence on skin conductance measures (Boucsein, 1992; Turpin et al., 1983).

Data Reduction

Physiological recordings were analyzed offline with customized software written by the second author in Matlab® (MathWorks, Natick, MA, USA). First, they were examined visually for artifacts which were excluded from further analysis. The record was then segmented into waking and sleeping, both on the basis of self-report, event markers, and an examination of the activity channel for cessation and resumption of activity. Waking periods were further divided into periods of usual activities and periods when the ART was performed. The results presented below are based on 1-min epochs of measurements from each channel (skin conductance, ambient temperature, physical activity) during each of these three periods (waking-usual activities, waking-ART, sleeping) unless otherwise indicated.

Raw skin conductance (SC) data was filtered using a zero-phase, order 10 low-frequency Butterworth filter with a cutoff frequency of 0.05 Hz. Skin conductance (SC) yielded four measurements: (1) mean skin conductance level based on 1-min means of filtered SC, (2) mean skin conductance variability based on within-1-min standard deviations of filtered SC, (3) mean number of non-specific skin conductance fluctuations (NSFs) in 1-min epochs defined as $+0.01 \mu\text{S}$ (iemens) inflections in the first derivative of filtered SC between consecutive data points, and (4) mean square successive differences (MSSD) based on the raw SC data sampled down to 4 Hz (throughout time periods of waking-usual activities and sleeping) in an attempt to replicate Hoehn-Saric's (2004) ambulatory findings who calculated MSSD separately for every epoch of 6 minute raw SC data sampled at 4 Hz. The last three measures represent different SC variability measures. Number of NSFs best reflects traditional practice but fails to take into account amplitude, whereas 1-min SC standard deviations and MSSD are affected by both number and amplitude of SC fluctuations. The Spearman correlations between these different SC variability measures were all significant at the 0.01 level, Spearman's rhos ranging from 0.70 to 0.98. Because of this redundancy, we included as primary measures only the customary NSFs measure (3) and the MSSD (4) to replicate the above mentioned study, and not the SC standard deviation measure (2).

Psychological measures included ratings on the current emotional state taken at three time points during the 24-hour measurement period as well as before and during the last min of each of the four repetitions of the ART. The within-subject mean ratings on the current emotional state questionnaire for the adjectives "anxious", "sad", "relaxed", "sleepy", "worried", and "tense" were calculated for waking-usual activities and waking-ART (except for "sad" which was not available for the ART) separately.

Statistical analysis

Psychophysiological data were analyzed using linear mixed models as recommended by Bagiella, Sloan, and Heitjan (2000), following a top-down strategy (see West et al., 2007). Data were analyzed from the three measurement periods: waking-usual activities, waking-ART, and sleeping. Marginal models (without any random effects specified) were fitted by maximum likelihood with an unstructured covariance matrix for the residuals. Primary measures were tested using one-tailed and secondary measures using two-tailed significance tests. SPSS 16.0.2 (SPSS Inc., Chicago, IL) was used for these computations.

Demographic and self-report measures—Study participants were compared on several demographic and clinical variables. Continuous and normally distributed measures were analyzed using independent-sample *t* tests. If the assumption of normality was violated, non-parametric Wilcoxon rank-sum tests were calculated. Differences in categorical variables were tested with χ^2 tests of Fisher's exact tests. Feeling "anxious" was a primary psychological measure since we hypothesized that PD patients would feel more anxious during waking than controls. Other measures, such as feeling "sad" or "worried" were secondary, exploratory measures.

Psychophysiological measures—Both pooled and sequential analyses were made. (A) Within-subjects means were calculated based on all 1-min measurement epochs within the waking and within the sleeping periods (except for the MSSD which were based on the re-sampled raw SC for these periods). Primary variables for hypothesis testing were the means of SCL, number of NSF's, and MSSD. These variables were tested for (a) period differences (waking-usual activities vs. sleeping), and (b) group differences using marginal models with main effects for group and time, and adjusting for the effects of age, gender, mean temperature, mean activity and the use of antidepressant medication. Group by period interactions were included in the model if they significantly improved the fit (tested by performing ML-based likelihood ratio tests). In addition, activity, another primary variable, was tested (one-tailed) for group differences during sleeping, adjusting for the same covariates except for activity. Bonferroni correction was applied when necessary. Cohen's *d* was calculated using *t* values and degrees of freedom [$d = 2t/\sqrt{df}$].

(B) Sequential analyses took into account the temporal sequence of SCL within subjects. (1) Ascending and descending run lengths of continuous epoch-by-epoch ascent or descent for 1-min epochs were calculated for waking-usual activities and sleeping. The $n + 1^{\text{st}}$ epoch was considered a continuation of an ascending (descending) run if its value was *greater* (*less*) or equal than the value of the n^{th} epoch. Once a next value interrupted this run, the length in min (derived from the number of epochs) of this run was calculated and the run length counter was reset to zero. The ascending run length was considered an indicator of prolonged periods of steadily increasing sympathetic activation or panic-like symptoms, while descending run lengths might indicate steadily decreasing activation or relaxation. (2) Linear and higher order regressions for consecutive 1-min mean SCL were calculated for sleeping. (3) The slopes of decline in the SCL 1-min means over the 8-min sitting periods of the ART combined over the four repetitions were calculated for each subject.

Results

As shown in Table 1, groups did not differ in age, gender, BMI, or race. PD patients reported having experienced 4.5 full-blown panic attacks and 17.4 limited symptom attacks during the past month, and a total PDSS sum score of 14.7 (± 4.2). Compared to controls, they were more depressed by the Beck Depression Inventory (BDI), more anxious by the Beck Anxiety Inventory (BAI), more agoraphobic when alone or accompanied as indicated

by the Mobility Inventory for Agoraphobia (MIA), and had more sleeping problems by the Pittsburgh Sleep Quality Index (PSQI). Smaller sample sizes for the questionnaire data were mostly due to missing data on more than an acceptable number of individual items in the respective questionnaires (carefully following the guidelines given by the authors) that prevented the calculation of total scores.

Fifty-nine percent of the PD group were diagnosed as PD with Agoraphobia. Forty-one percent of the PD group had other comorbid diagnoses: Major Depressive Disorder, 4; Generalized Anxiety Disorder, 3; Specific Phobia, 2; Posttraumatic Stress Disorder, 2; Obsessive Compulsive Disorder, 1. None of the controls had a history of PD or any other axis I disorder.

Four PD patients were taking benzodiazepines regularly at the time of testing and two as needed, from which they were discouraged during the monitoring. On a regular basis, 5 were taking selective serotonin reuptake inhibitors (SSRI's), 2, other antidepressants (venlafaxine, mirtazapine), 1, buspirone, and 1, a beta-blocker. None was taking tricyclic antidepressants or antihistamines. None of the control group was taking a psychoactive drug and none of the subjects in either group was taking sleeping aids. In the following, subjects described as taking "antidepressant medication" are the 5 PD patients who were regularly taking SSRI's and the 2 who took other antidepressants (including 1 subject also taking buspirone).

Tests of our hypotheses

Mean SCL during day 1 was significantly higher than during day 2 but there was no group by day interaction in waking mean SCL. The data from both days were then collapsed.

Hypothesis 1 (waking differences)—As shown in Table, the mean skin conductance levels were significantly higher in the PD group than in the control group and this effect further increased after adjusting for the effects of gender, age, mean temperature, mean activity, and antidepressant medication. In the adjusted model, mean SCL was significantly decreased by age [$F(1,47.8)=5.3$, $p<0.05$] and the use of antidepressant medication [$F(1,46.6)=4.8$, $p<0.05$]. Women tended to have higher mean SCL [$F(1,47.4)=3.6$, $p=0.06$], whereas mean temperature and activity did not affect mean SCL. The mean numbers of NSFs and the MSSD sampled at 4 Hz as in Hoehn-Saric's (2004) paper did not differ significantly between the groups, although the number of NSFs tended to be higher in the PD patients after adjusting for the covariates. PD patients reported being more anxious than controls when performing usual activities ($p<0.005$).

Hypothesis 2 (ART)—During the ART on the other hand, neither the mean nor the slope of SCL [$PD=C=-0.3$, $F(1,49)=0.0$, $p>0.05$] differed between the groups. The same was true for the number of NSFs. PD patients reported being more anxious than controls when trying to relax ($p<0.005$).

Hypothesis 3 (sleeping differences)—Since both waking and sleeping periods were tested in the same model with period as a factor (factor levels were waking and sleeping), the results described above under hypothesis 1 also apply to the sleeping period except for the self-report, which only was available for waking periods. There was no interaction between Group and Period (levels waking and sleeping). Mean activity during the night was significantly higher in the PD group than the control group, which weakened after adjusting the model for age, mean temperature, gender and antidepressant medication.

Exploratory tests

During *waking*, PD patients were also less relaxed ($p<.05$) and more worried ($p<.005$), tense ($p<.005$), and sad ($p<0.05$) than controls. To examine whether waking state anxiety (“feeling anxious”) or state depression (“feeling sad”) might explain the positive mean SCL findings, marginal model analyses were conducted in the PD group for each time period separately, adjusting for the effects of antidepressant medication, gender, age, mean temperature, and activity. Higher state anxiety was associated with higher mean SCL during waking [$F(1, 21)=7.2$, $p<0.05$, Cohen’s $d=1.2$]. Higher levels of daytime state depression were associated with higher mean SCL during sleeping [$F(1,21)=5.8$, $p<0.05$, Cohen’s $d=1.0$]. Both relationships represent large effects.

When performing similar analyses in the PD group that aimed to elucidate the role of agoraphobia, no significant relationships with mean SCL could be found – neither when comparing PD patients with and without agoraphobia (mean Cohen’s $d=-0.7$ for waking and sleeping), nor considering MIA questionnaire scores (when accompanied: mean Cohen’s $d=-0.7$, when alone: mean Cohen’s $d=-0.6$). Although not significant, all these effects were of medium size and pointed towards an inverse relationship between the level of agoraphobia and SCL, i.e., more agoraphobic symptoms corresponded to a lower SCL.

Next, the influence of acute panic symptoms (as opposed to tonically elevated anticipatory anxiety) on mean SCL was examined. Self-report data on panic attacks during waking and sleeping and subjective sleep disturbance was limited due to missing data. Only 15 PD patients (68%) and 19 controls (66%) provided self-reports on the number of panic attacks. During *waking*, 3 out of these 15 PD patients reported having had 1 panic attack, 1 reported 2, and 1 reported 3 attacks. One PD patient experienced a nocturnal panic attack, while none of the controls reported having had panic attacks during either sleeping or waking. The number of daytime attacks was significantly higher in PD patients ($p<.05$, two-tailed Fisher’s exact test). Within the PD group, no significant relationships could be found between the number of daytime panic attacks and waking mean SCL (Cohen’s $d=0.7$) or the number of nocturnal panic attacks and sleeping mean SCL (Cohen’s $d=-0.3$).

To determine whether subjective accounts of sleep disturbance could have influenced the mean SCL, self-report data on sleep were examined, but here as well, missing data limits generalizability. There were no differences in reported sleep duration, number of nocturnal awakenings, the restfulness of sleep, or daytime sleepiness. Length of the sleeping periods did not differ between groups, with a mean of 515 min in the PD group and 495 min in the control group. PSQI scores within the PD group were not associated with mean SCL during any time period (mean Cohen’s $d=-0.5$ for waking and sleeping) after adjusting for age, gender, mean temperature, activity, and antidepressant medication.

Finally, mean SCL was examined for periods of steadily increasing or decreasing activation which could indicate abnormal modulation of sympathetic arousal in PD patients. During *waking*, groups did not differ in either ascending or descending run lengths of 1-min epochs of SCL. Both groups had a steep decline in SCL over the first 30 min of the *sleeping* period, and then a slower decline. These declines were approximately parallel in the two groups as confirmed by regression analyses. However, an almost significant group by period interaction [$F(1,47.3)=3.6$, $p=0.06$] was related to shorter descending run lengths of SCL in PD patients during *sleeping* (post-hoc test [$F(1,49.2)=4.5$, $p<0.05$, Cohen’s $d=0.6$]). In other words, PD patients had more frequent interruptions in the downward descent of SCL measures than controls.

Discussion

Our hypothesis that during waking periods, skin conductance levels (SCL) and measures of non-specific skin conductance fluctuations would be higher in PD patients was partly confirmed in that mean SCL was elevated during waking (large effect), but measures of SC variability were not. Self-reports documented that these patients experienced more anxiety which itself was associated with higher mean SCL within the PD group (large effect). Figure 1 indicates that this difference in mean SCL disappeared on the second day of recording although no significant interaction between group and day was found. The finding of higher mean SCL during waking anxious states is in agreement with several laboratory studies (e.g., Braune et al., 1994; Hoehn et al., 1997; Parente et al., 2005) but not with the ambulatory study of Hoehn-Saric et al. (2004), and several laboratory studies (e.g., Argyle, 1991; Blechert et al., 2007).

Methodological differences that may have contributed to the inconsistent findings of previous laboratory studies were explored in our data. In our PD group, although more depressed than controls, there was no significant relationship between state depression and mean SCL during waking, unlike in older studies (Argyle, 1991; Ward et al., 1983). Similarly, the level or diagnosis of agoraphobia did not significantly influence mean SCL. The observed relationship was inverse, which could be interpreted as the more agoraphobic PD patients successfully reducing their anxiety by avoiding anxiety-provoking situations. Unfortunately, our self-report data were inadequate for testing this interpretation. Taking antidepressant medication had the effect of reducing the mean SCL in PD patients, while state anxiety and daytime panic attacks, increased mean SCL, although the last result was not significant. Thus, some discrepancies between previous studies may have been caused by varying levels of agoraphobia and different medication policies. The former might also account for the null findings in Hoehn-Saric's ambulatory study (2004) since they did not assess for comorbid agoraphobia, which might have reduced the mean SCL of their PD patients.

Despite a trend in the number of NSFs (medium-sized effect), measures of SC variability did not significantly differ between the groups: neither the number of NSFs nor the MSSD, which in the Hoehn-Saric et al. (2004) ambulatory study was significantly lower in the PD group. Our MSSD result must be interpreted with caution because of non-convergence of the statistical model. A failure to find significantly higher SC variability in the presence of higher mean SCL was reported previously (Parente et al., 2005). According to a recent functional magnetic resonance imaging (fMRI) study, different brain structures regulate tonic and phasic SC activation (Nagai et al., 2004). SCL, a tonic measure, had a closer relationship with brain regions associated with anticipatory anxiety (for a discussion, see Parente et al., 2005). Alternatively, the lack of significant SC variability differences may be a consequence of high, uncontrolled SC variance unrelated to anxiety. Unexpected events, interpersonal engagement, and positive and negative emotions of all kinds may affect SC. These factors also may have interrupted descending runs of SC, a possible measure of relaxation during daily activities, and obscured waking differences in the ability of patients and controls to relax.

However, even when these uncontrolled factors were minimized during the ART, during which patients sat quietly and tried to relax, no group differences were found in either mean SCL or its rate of decline. This is contrary to our second hypothesis that during waking periods, PD patients would be less able to relax and physiologically deactivate than controls. These findings can be interpreted as meaning that PD patients can relax just as well as non-anxious controls or that skin conductance is not a valid measure of relaxation. Results might have been different at higher anxiety levels: although more anxious than the control group,

almost 90% of our PD patients rated the intensity of their state anxiety in the lower one-third of the scale both during the ART and usual activities. On the other hand, 5 of our 22 PD patients reported a panic attack sometime while being monitored, which is quite a few considering that investigations of PD usually have an entrance criterion of no more than one attack per week. That we found higher mean SCL under daily-life conditions but no differences during a short and relatively standardized test of quiet sitting and relaxing, again calls into question the validity of the ART.

Our third hypothesis, that the differences postulated for waking would be present in some form during sleeping periods, was confirmed. During sleep, PD patients had higher mean SCL than controls. Both groups had steep declines in SCL from waking levels during the first 30 min followed by slower parallel declines afterwards. Exploratory analyses revealed that the failure of PD patients to achieve lower levels could be related to more frequent interruptions of deactivation as evidenced by shorter descending SCL runs. They also pointed to the potentially aggravating role of comorbid daytime depression, which increased the mean SCL within the PD group on the night of the recording (a large effect). Waking state anxiety and agoraphobia did not significantly affect mean SCL. PD patients rated themselves on the PSQI as having slept more poorly during the past month, but PSQI scores were uncorrelated with mean SCL on the recording night. In spite of SC evidence of poor sleep, PD patients did not rate themselves as sleeping more poorly on the night of recording; both results, however, were weakened by missing data. Higher activity levels during sleep in the PD group indicated sleep disturbance, but this difference disappeared after adjusting for gender, age, mean temperature, and antidepressant medication. Perhaps processing of conditioned interoceptive threat cues during sleep gave rise to bursts of sympathetic autonomic activation as part of a conditioned anxiety response, and interrupted SCL descent. Such bursts could be the basis of nocturnal panic attacks, but if so, they were generally below awareness in that patients did not report poorer sleep than controls on the recording night, and only 1 of 22 PD patients reported having had a panic attack.

This study is limited in several ways. First, the advantages of ecologically valid ambulatory physiological measures must be weighed against the imperfect control of disturbing factors such as activating interpersonal interactions. Better control of these factors might have allowed additional group effects to emerge. Second, we measured only skin conductance to assess anxiety in PD. Heart rate, respiratory sinus arrhythmia, respiratory variability, and end-tidal pCO₂ might have informed us whether the skin conductance findings were part of a general pattern of stress activation. Polysomnography would have been helpful, since we cannot determine how much of the sleep period our subjects actually slept and whether the interruptions we observed were associated with EEG changes in specific sleep stages. Skin conductance has rarely been recorded during sleep, and it is conceivable that it can register sleep disturbances in anxiety disorders that are missed by conventional polysomnography. Thirdly, restricting our patient sample to patients not taking any medications would have excluded their possible interfering effects but would have impaired the representativeness of any findings, since in developed countries unmedicated patients can be an atypical subgroup. Apparently, the antidepressants taken by our PD patients lowered their SCLs without producing a clinical remission in panic. We did not do blood or urine testing to confirm patients' medication use, which might have revealed reporting failures. Fourthly, since we did not examine patients with other anxiety disorders, we do not know the extent to which our results are specific to the diagnosis of PD. Perhaps increased SCL is a general characteristic of anxiety disorders or is associated with elevated levels of anxiety regardless of diagnosis. Furthermore, as our sample was relatively small, its statistical power for our primary hypotheses was limited. With more participants, statistical tests at a trend (e.g., number of NSF's) probably would have been significant. This particularly applies to our self-report data, which was often missing.

In summary, individuals with current PD show evidence of sustained sympathetic activation, both during the day during their usual activities and at night during sleep. Elevated activation while awake is in accordance with observations that many PD patients suffer from sustained anxiety between panic attacks, which has been ascribed to anxious anticipation of future attacks. Elevated SC activation during sleep is in accordance with patient complaints of disturbed sleep, which have been hard to document with conventional polysomnography not measuring skin conductance. Recording skin conductance outside the laboratory in natural settings shows promise for the assessment of PD severity and could be useful in therapy outcome studies as a supplement to structured interviews and questionnaires. Future ambulatory studies should control for the potentially confounding effects of depression, agoraphobia, and medication.

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Figure 1. Mean SCL across PD and control subjects for each 1-min epoch synchronized by onset of sleeping period. At least 10 valid observations per group were required for included time epochs.

Table 1

Laboratory studies measuring electrodermal activity in panic disorder patients.

Study	Sample	Medications allowed	Setting	Procedure	Results		
					SCL	NSFs	Other measures
Lader & Wing (1964)	20 PD (pre-DSM-III, 3 with AG sxs), 20 HC	?	alone in dimly lit sound-attenuated room	<p>a. resting baseline (11 min)</p> <p>b. auditory startle (20 min) + 1 min</p>	logSCL (a) last min: PD > HC (b) except very beginning: PD > HC	(a,b) PD > HC	(b) 1 st log SCR PD = HC other log SCR PD < HC
Lader & Mathews (1970)	3 PD (pre-DSM-III, AG sxs not established)	?	?	recording during spontaneous panic attacks	marked and rapid increase, slow decline		
Freedman et al. (1984)	8 PD (DSM-III, AG dx not established), 9 HC	?	connected to IV line	<p>3 sessions (5–10 days apart) of panic attack provocation:</p> <p>a. resting baseline (10 min)</p> <p>b. IV dextrose (10 min)</p> <p>c. IV infusion of sodium lactate/isoproterenol/placebo (randomized) until panic attack occurred or 20 min</p> <p>d. IV dextrose (10 min)</p> <p>e. resting baseline (10 min)</p>	(a,b,c,d) PD = HC; (e) PD > HC; panic attacks (PA) = no PA		
Roth et al. (1986)	37 AG with panic attacks (DSM-III), 19 HC	no: TCAs or MAOIs	sound-attenuated room, 24 AG alone, 13 AG with companion	<p>a. resting baseline (15 min)</p> <p>b. habituation (10 min, to 18 identical tones, 1 different tone)</p> <p>c. startle white noise bursts of different intensities (10 min)</p> <p>d. resting baseline with 20 white noise bursts during min 3 (5 min)</p>	logSCL (a,d) AG > HC, habituated (b) AG > HC, habituated faster in HC (c) AG > HC, habituated faster in HC	(a,d) AG > HC (b, c) AG = HC	SCR: (b) total number: AG > HC (c) magnitude, recovery: AG = HC
McNally et al. (1989)	24 PD (DSM-III-R, 18 with AG), 24 HC	?	?	<p>a. resting baseline (10 min)</p> <p>b. word rating task</p> <p>c. exercise or quiet sitting</p>		(a,b,d) PD = HC (c) PD (exercise), HC (quiet sitting) > PD	

Study	Sample	Medications allowed	Setting	Procedure	Results		
					SCL	NSFs	Other measures
				d. recall task (3 min)		(quiet sitting), HC (exercise)	
Roth et al. (1990)	38 PD or AG with panic attacks (DSM-III, 12 with MD episodes), 29 HC	no: benzos, TCAs	alone in sound-attenuated room	a. several tasks including hyperventilation b. habituation of orienting SCR to auditory tones (10 min)	(a) not reported (b) PD > HC (logSCL)	(b) PD > HC	(b) time to habituation: PD > HC (b) slope of SCL decline: PD < HC
Argyle (1991)	66 PD (DSM-III, 37 with AG, 21 with MD), 10 HC	yes: benzos and stable TCAs (7 patients)	alone in big or small room	resting baselines (16 min each) in a. big room b. small room (all HC + 10 PD) in randomized order	(a, b) min 15, 16; PD = HC (a) logSCL min 15, 16; MD < non-MD		
Hoehn-Saric et al. (1991)	18 PD (DSM-III-R, AG dx not established), 18 HC	no to all	in dimly lit room, alone?	a. resting baseline (10 min) b. divided attention task (5 min) c. risk taking task (5 min) d. resting baseline (5 min)	(a,b,c,d) PD = HC		range of SCL: (b,c) PD < HC (a,d) PD = HC
Birket-Smith et al. (1993)	12 PD (DSM-III-R), 11 AG with panic attacks, 12 HC	yes: benzos, TCAs, SSRIs, and antipsychotics	quiet room, alone?	a. habituation to auditory stimuli b. resting baseline	(b) SRL: PD = AG = HC, medicated = not medicated	(a) PD = AG = HC	(a) SRR habituation rate: PD > HC
Braune et al. (1994)	27 PD (DSM-III-R, 12 with AG), 10 HC	no to all	quiet, well-lit room, alone?	resting baseline (15 min)	PD > HC		
Hoehn et al. (1997)	33 PD (DSM-III-R, 19 with AG), 10 HC	no to all	room?, alone?	a. resting baseline (15 min), b. 4× stress exposure reactivity: frightening video, mental arithmetic, panic attack video, improvised speech (3–4 min) c. 4× recovery (3 min) d. final resting baseline (17 min)	(a–d) PD > HC		(b, panic attack video) SCR: PD > HC

Study	Sample	Medications allowed	Setting	Procedure	Results		
					SCL	NSFs	Other measures
Roth et al. (1998)	14 PD (AG dx not established), 15 HC	no to all	alone in small sound-attenuated room	relaxing (10 min) (after talking for 4 min)	PD = HC		fractional SCL decline: PD < HC goodness of fit over log time (inverse of variance): PD < HC
Wilhelm et al., (2001)	16 PD (DSM-III-R, AG dx not established), 19 HC	no to all	alone in large, quiet temperature controlled room	quiet sitting (30 min)	PD = HC	PD = HC	
Alpers et al. (2005)	21 driving phobics (11 with history of panic attacks, AG dx not established), 17 HC	no to all	quiet sitting (a, e) alone in small room	<p>a. quiet sitting (7 min)</p> <p>b. approaching highway (10 min)</p> <p>c. driving exposure (60 min)</p> <p>d. return to lab (10 min)</p> <p>e. quiet sitting (7 min)</p>	(a-e) phobic > HC	(a-e) phobic > HC	
Parente et al. (2005)	14 PD, 16 medicated sx-free PD, 16 HC	yes: SSRIs, clomipramine	?	simulated public speaking	PD > medicated PD = HC	PD = HC	
Bleichert et al. (2007)	26 PD (AG dx not established, no MD), 32 HC	yes: SSRIs, SNRIs no: benzos, beta-blockers, sympatho-mimetic drugs, antipsychotic, TCAs	alone in small temperature and sound- controlled room	<p>a. quiet sitting (5 min)</p> <p>b. threat of shock (5 min)</p>			electrodermal sympathetic index = ESI (SCL, NSF's, SCRamp); (a,b) PD = HC b) ESI reactivity: PD = HC PD = HC medicated = not medicated

Abbreviations: PD = Panic disorder patient, HC = healthy control; AG = Agoraphobia; MDE = Major Depressive Episode Disorder; dx = diagnosis; sxs = symptom; TCAs = tricyclic antidepressants; MAOIs = monoamine oxidase inhibitors; benzos = benzodiazepines; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-noradrenaline reuptake inhibitors; IV = intravenous; SCL = skin conductance level; NSF's = number of non-specific fluctuations; SCR = skin conductance response; SRR = skin resistance response; ? = no information.

Table 2

Demographics and self-report measures

	PD (n=22)	Controls (n=29)	Statistic
Age	42.7 ± 15.0	42.1 ± 12.3	t(50) = -1.54 (NS)
Females	14 (64)	19 (66)	$\chi^2(1,38) = 0.02$ (NS)
BMI	26.1 ± 4.1	24.5 ± 4.2	t(50) = -1.34 (NS)
Racial Category			p=0.29, FET(NS)
Whites	11 (50)	20 (69)	
Asian	2 (9)	4 (14)	
Other	4 (18)	3 (10)	
Missing or declined	5 (23)	2 (7)	

	PD	n	Controls	n	Wilcoxon W
BDI (0–63)	13.5 ± 11.0	(18)	1.0 ± 4.0	(28)	421.5***
BAI (0–63)	20.5 ± 21.3	(14)	2.0 ± 5.0	(20)	245.0***
MIA alone (1–5)	2.4 ± 1.3	(18)	1.1 ± 0.3	(27)	408.5***
MIA accompanied (1–5)	1.9 ± 1.0	(19)	1.0 ± 0.1	(27)	407.5***
PSQI (0–21)	7.0 ± 5.0	(11)	4.0 ± 2.5	(21)	277.0**

Note. Values are expressed as mean ± SD or number (%) for the demographic variables, and as median ± interquartile range for the self-report measures. Group sizes vary for the self-report measures due to missing data. **Abbreviations.** NS = not significant,

**
p-value < 0.01,

p-value < 0.005, FET = Fisher's Exact Test;

BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, MIA alone = Mobility Inventory for Agoraphobia (subscale "when alone"), MIA accompanied = Mobility Inventory for Agoraphobia (subscale "when accompanied"), PSQI = Pittsburgh Sleep Quality Index; PD = Panic disorder group.

Table 3

Estimated marginal means of primary electrodermal measures and activity by period (model 1: waking and sleeping, model 2: ART, model 3: sleeping only).

		Mean (SE)		t ¹	df	p	d
	period	PD (n = 22)	Controls (n = 29)				
mean SCL (μSiemens)	Unadjusted	waking	7.8 (0.6)	6.9 (0.6)	-2.0*	49.6	<0.05 -0.6
		sleeping	3.2 (0.3)	2.3 (0.3)			
	Adjusted ²	waking	7.8 (0.6)	6.5 (0.6)	-2.9***	47.9	<0.01 -0.8
		sleeping	3.7 (0.4)	2.4 (0.4)			
mean nNSFs	Unadjusted	ART	6.9 (0.6)	6.0 (0.5)	-1.2	49	>0.05 -0.3
		ART	6.9 (0.6)	6.0 (0.5)	-1.1	49	>0.05 -0.3
	Unadjusted	waking	1.9 (0.2)	1.9 (0.2)	-0.4	48.9	>0.05 -0.1
		sleeping	0.3 (0.1)	0.3 (0.1)			
MSSD⁴ (4Hz)	Adjusted ²	waking	1.9 (0.2)	1.7 (0.2)	-1.6	48.6	0.06 -0.5
		sleeping	0.5 (0.1)	0.3 (0.1)			
	Unadjusted	ART	1.2 (0.2)	0.9 (0.1)	-1.3	49	>0.05 -0.4
		ART	1.2 (0.2)	0.9 (0.1)	-1.0	49	>0.05 -0.3
mean ACT	Unadjusted	waking	0.0 (0.0)	0.0 (0.0)	-1.2	90.9	>0.05 -0.3
		sleeping	0.0 (0.0)	0.0 (0.0)			
	Adjusted ³	waking	0.0 (0.0)	0.0 (0.0)	-1.0	101.1	>0.05 -0.2
		sleeping	0.0 (0.0)	0.0 (0.0)			

Abbreviations: SE, standard error; PD, panic disorder; p, p-value (one-tailed); SCL, skin conductance level; nNSFs, number of non-specific fluctuations; MSSD, mean square successive differences in SC; ACT, activity; ART, ambulatory relaxation test; d, Cohen's d.

¹Based on t statistics for contrast comparison.

²Adjusted for gender, age, mean temperature, mean activity, and antidepressant medication.

³Adjusted for gender, age, mean temperature, and antidepressant medication.

⁴Convergence not achieved. Results were based on the last iteration. Thus the validity of model fit is uncertain.