
Autonomic Characteristics of Agoraphobia with Panic Attacks

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We compared electrodermal and heart rate measures of autonomic activation between patients meeting DSM-III criteria for agoraphobia with panic attacks and controls in terms of tonic level, reactivity to various types of stimuli, recovery, habituation, and spontaneous variability. The most striking differences between groups in the laboratory were higher tonic levels of skin conductance and heart rate among patients. Patients' heart rates were also tonically elevated in a test situation outside the laboratory. Certain measures of habituation and spontaneous variability also differed between groups, but there were only weak and inconsistent differences in reactivity to, or recovery from, stimuli with diverse qualities of novelty, startliness, intensity, or phobicity. The elevated activation levels may be signs of a chronic state or may be phobic responses to the testing situations. A minority of patients failed to show these elevated levels.

Introduction

Much attention has been focused recently on the biology of agoraphobia and panic attacks (for summaries see Klein 1981; Ballenger 1984; Margraf et al. 1986), yet there are few studies of autonomic activation (arousal) in these patients. This is especially surprising, as DSM-III criteria for anxiety include lists of somatic symptoms, many of which are the subjective counterparts of signs of activation. Physiological measurements complement subjective and clinical assessment, being free of certain biases possible in other kinds of reports and providing information about biological functioning that is otherwise hidden.

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We report a study of 37 agoraphobics with panic attacks who were recruited for a treatment study comparing behavior therapy, imipramine, and their combination. The effects of those treatments are reported in detail in another paper (Telch et al. 1985). Prior to treatment, we measured heart rate and skin conductance level and reactivity parameters in these agoraphobics and controls in the laboratory and heart rate ambulatorily in a test situation outside the laboratory. Theoretically, patients might differ from controls in tonic level of activation, phasic reactivity or speed of recovery from reactivity, habituation, or variability. Furthermore, enhanced reactivity might occur to nonphobic stimuli in nonstressful settings, or it might be restricted to phobic stimuli or stressful settings. We explored these possibilities with nonphobic stimuli that varied in novelty, intensity, and startlingness and by exposing subjects to a stimulus situation that was phobic for the agoraphobics, namely, walking through a shopping mall.

On the basis of patients' reports of their anxiety experiences, we made a series of predictions: that they would have higher tonic levels of activation, as their anxiety seldom abated completely; greater reactivity, as they were overly sensitive to adverse events; slower recovery and habituation, as they had difficulty relaxing; and that they would have more variable activation, as they suffered from sudden unpredictable increases in anxiety. There is already some experimental support for these predictions in a series of laboratory studies (Lader and Wing 1964, 1966; Lader 1967) in which certain types of anxious patients, including those diagnosed as having an "anxiety state" or agoraphobia, had more slowly habituating skin conductance responses and levels than controls, as well as tonically higher heart rates and skin conductance. Lader and Mathews (1968) postulated that high levels of sustained anxiety in patients could be caused by a positive feedback loop in which successive stimuli produce arousal increases that habituate more slowly as the arousal level increases.

We were less sure to which classes of stimuli agoraphobics would be more reactive or habituate more slowly. We assumed that they would react more than controls to agoraphobic stimuli and thought it likely that they would habituate more slowly to aversive nonphobic stimuli (Lader and Wing used 100-dB tones), but we were uncertain if they would react more to the novelty of the mild tones of the standard orienting response paradigm in which schizophrenics are much less reactive than controls (Öhman 1981; Bernstein et al. 1982). Exaggerated orienting responses are neither a usual anxiety symptom nor a consistent experimental finding in variously defined groups of anxious patients (Öhman 1981), however, a recent neuropsychological theory strongly implies that orienting responses should be more active in at least some kinds of anxiety (Gray 1982a). We were also uncertain if our agoraphobics would react more strongly to stimuli, which by their rapid onset specifically elicit startle. Heightened startle responses figure in the DSM-III criteria for post-traumatic stress disorder and generalized anxiety disorder, but are not mentioned among the symptoms of panic attacks.

Although we predicted that agoraphobics would be more reactive to external events than controls, we realized that, alternatively, agoraphobic anxiety and activation might be driven primarily by internal events. Internal events or states could produce attack-like or sustained anxiety when perceived, or directly and automatically without prior awareness. The importance of internal factors would be favored by evidence of normal reactivity to stimuli in agoraphobics; greater reactivity would be less decisive because that could be a secondary consequence of an internal derangement.

Methods

Subjects

People suffering from agoraphobia with panic attacks were recruited through advertisements. To participate in the study subjects had to meet the definition for agoraphobia with panic attacks in the third edition of the *Diagnostic and Statistical Manual for Mental Disorders* (American Psychiatric Association 1980). Subjects already in treatment with tricyclic antidepressants or monoamine oxidase (MAO) inhibitors were also excluded. A spouse or friend had to be available to take part in the subjects' behavioral treatment. The 37 patients who entered the study included only two men, had a mean age of 41.5 years (range 21–63), and had had agoraphobic fears for a mean of 12 years. Two patients were black.

Controls were also recruited by advertisement. They were selected to match the patients by age, sex, and race and were paid for their participation. We tried to restrict our control sample to people who were free from psychic complaints, especially ones related to anxiety and phobia. Subjects were interviewed by a psychiatrist prior to testing, who excluded about a quarter of the applicants for history of anxiety, social phobias, depression, physical symptoms possibly related to anxiety or depression, or signs of anxiety during the interview. An additional subject was rejected because of several high scores on the Symptom Check List-90 (SCL-90) questionnaire (revised version) (Derogatis 1977). The 19 controls who were finally selected included two men and two blacks and had a mean age of 41.3 years (range 22–59).

The general nature of the study and its specific procedures were explained to each participant, and written informed consent was obtained before proceeding.

Psychological Evaluation

Subjects filled out a number of questionnaires, including the SCL-90, with a time frame of the past 6 months, the Fear Questionnaire (Marks and Mathews 1979), the 21-item Beck Depression Inventory (Beck et al. 1961), and the Zung Self-Rating Depression Scale (Zung 1965). Patients kept a diary in which they recorded activities and any panic attacks during the period of the study. The state scale of the Spielberger State-Trait Anxiety Inventory (Spielberger et al. 1970) was given to subjects at the time of the laboratory test battery. During the test walk in the shopping center, performance was scored by observers, and subjective anxiety was reported on questionnaires.

Psychophysiological Testing

Laboratory Battery. Subjects were tested on a battery of four paradigms in a single session before any treatment began. All subjects were told to discontinue any psychoactive medication (generally antianxiety agents) 3 days before laboratory testing. A number of the agoraphobics found that impossible: 6 had taken antianxiety agents within 12 hr of testing. Three others had imbibed moderate quantities of alcohol shortly before arriving at the laboratory.

Testing took place in a sound-attenuated booth. Most of the agoraphobics were accompanied to the laboratory by a companion in whose presence they felt reassured, and in 13 cases, at the plea of the agoraphobics, this companion was allowed to sit in the

booth with them. In these and other cases, agoraphobics often insisted that the door to the booth remain open. After entering the booth, and before recording began, subjects filled out the state anxiety questionnaire of the Spielberger State-Trait Anxiety Inventory. Skin conductance was recorded from a pair of Ag/AgCl disc electrodes, 0.8 cm² in area, both placed on the thenar eminence of the left hand. The electrode medium was a mixture of creamy ointment and physiological saline, as recommended by Fowles et al. (1981). Subjects rinsed their hands with water alone before the electrodes were applied. The skin conductance transducer applied a constant 0.5 V across the electrodes. The electrocardiogram was recorded from electrodes over the 10th rib on the midclavicular line and over the manubrium of the sternum. During all paradigms, subjects wore earphones through which 40-dB sound pressure level (SPL) noise was given continuously to mask extraneous sounds. The paradigms were given in the following order:

1. Baseline 1 (5 min). No stimuli were given. Subjects were instructed to sit quietly with their eyes open and to relax.
2. Habituation (10 min). This paradigm is a version of the standard orienting response paradigm that has been used in many investigations of psychiatric patients (Öhman et al. 1981; Bernstein et al. 1982). Nineteen 1-sec tones were given with random interstimulus intervals (ISIs) uniformly distributed over a 24-45-sec range. The rise and fall times of the tones were 25 msec. All except tone 17 were 1000 cycles/sec and 75 dB SPL. Tone 17 was 600 cycles/sec and 70 dB. Subjects were told that they would be hearing tones, but that they did not have to do anything.
3. Intensities (10 min). This paradigm delivers stimuli that are known to elicit startle responses (Roth et al. 1984), i.e., responses whose biological anlage is distinct from that of orienting responses (Graham 1979). Fifty-millisecond white noise pips, with a rise and fall time of 1 msec, were given with random ISIs distributed in the range of 12-17 sec. The pip intensities were either 75, 90, or 105 dB SPL. A total of 37 stimuli was given. The first was 90 dB, and the rest were randomized in 12 groups of 3, each group containing one stimulus of each intensity. Subjects were told that they would be hearing noises but that they did not have to do anything.
4. Baseline 2 (with noise) (5 min). Stimuli were given only during the third minute of the run. The stimuli were 1-sec, 90-dB white noise bursts with 1-msec rise and fall times. A total of 20 were given with a 3-sec ISI from onset to onset of consecutive stimuli. Subjects were to sit quietly and relax with their eyes closed.

For subjects who had elevated hearing thresholds as determined by audiometry, tone and noise intensities were increased to the degree necessary to make them equivalent to the prescribed SPLs for normal hearing subjects.

Ambulatory Monitoring. On a different day from the laboratory session but also before any treatment, heart rate was monitored before and during a Behavioral Approach Test (BAT) using a portable microcomputer programmed to store smoothed running heart rate averages at 1-min intervals. This device and its use are described in more detail in Taylor et al. (1983). The BAT required the subjects to walk a course consisting of 12 stations through a large shopping mall and to return to the starting point. The stations were shops or other landmarks. A subject who reached all stations would walk a total of 680 m, taking about 10 min.

The computer monitor was attached in the clinic and was worn throughout the BAT.

The subjects first sat in a chair in the clinic for 10 min so that their sitting heart rates could be recorded. Then they were driven to the shopping mall, about 10 min away, where they were given a map of the BAT course and oriented to the locations of the stations. At a signal from a timekeeper, they proceeded alone along the course without pausing as far as they could go. At each station reached, they rated themselves for anxiety on a 0–10 scale with 0 representing complete calm and 10 extreme anxiety.

The results of a second round of laboratory and ambulatory testing during treatment will be reported elsewhere.

Data Analysis

Laboratory Battery. For baseline 1, the mean skin conductance level (SCL), number of nonspecific fluctuations (NSFs), and mean heart rate level (HRL) were calculated for each of the five 1-min periods. Heart rate variability was calculated for the entire 5-min run. Both skin conductance and heart rate measurements were made automatically by computer. Our programs edited all laboratory and ambulatory data for artifacts due to electrode displacement and sudden beat-to-beat heart rate changes suggesting arrhythmias. Skin conductance was sampled every 50 msec. The occurrence of an NSF was defined as an increase in SCL of 0.05 microsiemens (μ S) occurring within 3.5 sec after a change in SCL slope of at least 0.01 μ S/sec from negative or zero values to a positive value. The time point where the change in slope first meets these criteria is the "onset point," a point also used in defining the skin conductance response as explained below. Heart rate variability measures included standard deviations, successive difference mean squares (Heslegrave et al. 1979; Wastell 1981), and number of reversals (Wastell 1981). The first two measures were calculated on a beat-to-beat basis [both in terms of R–R interval and beat per min (bpm)]: 10-sec means (bpm) and 60-sec means (bpm). The number of reversals was calculated on a beat-to-beat basis.

For habituation and intensities, SCLs were calculated separately for each stimulus as the SCL average over a 0.5-sec prestimulus period. HRLs were averages over a 9-sec prestimulus period for habituation and over a 2-sec prestimulus period for intensities for each stimulus. A skin conductance response (SCR) was defined as a response with an onset point 1.0–4.0 sec after stimulus onset whose amplitude reaches 0.05 μ S within 3.5 sec after this point. The number of SCRs to habituation was the number of responses before three consecutive failures to respond. As the stimulus on trial 17 was dishabituating, this measure was only calculated to trial 16. The maximum number of trials to habituation was 13, as that was the highest trial number that would allow the testing of three more trials before reaching trial 17. Our time window for detecting SCRs and criteria of three failures are commonly used, but may overestimate the number of SCRs to habituation in the presence of NSFs (Levinson and Edelberg 1985; Levinson et al. 1985). A second SCR habituation measure, change of SCR magnitude, was calculated for the habituation paradigm by the method of Lader and Wing (1966): the parameters of the linear regression line relating log SCR amplitude and log trial number were determined for each subject over the range, beginning with trial 2 and ending with the third consecutive failure to respond. (SCR magnitude measures include zero values or failures to respond in their calculation, whereas SCR amplitude measures exclude zero values.) In addition, for SCRs in the habituation paradigm, the amplitude, rise time, peak latency, one-quarter recovery time, one-half recovery time, and the ratio of (number of SCRs/sec)/(NSFs/sec + 1) were calculated. Recoveries greater than 10 sec were considered to be invalid. For the

SCR/NSF ratio, the time window from 1.0 to 4.0 sec after the first 16 stimuli was searched for SCRs, and 17-sec time window before each of these stimuli, NSFs.

For habituation and intensities, stimulus-synchronized heart rate responses (HRRs) were calculated for 0.5-sec units, beginning 2 sec before the stimulus to 8 sec after it, using the method of Graham (1978). The amplitude of HRR acceleration (A) was calculated as the maximum increase in HRR between a 1.0-sec prestimulus baseline and the +2-+5-sec range. The amplitude of early HRR deceleration (D1) was calculated as the maximum decrease between the prestimulus baseline and the +0.5-+4-sec range for habituation and the 0.5-+2.5-sec range for intensities. The late HRR deceleration (D2) was measured in the 4.5-8-sec range for habituation and the 4.5-7-sec range for intensities. These ranges were based on the HRR literature and on inspection of group averages of HRR. The latencies of D1, A, and D2 were also measured.

For baseline 2, the same measurements were made as for baseline 1, except for those of heart rate variability, which would be confounded with the effects of the noise. In addition, the amplitude of the maximum rise in SCL following the onset of noise in minute 3 was measured. Amplitude was measured with respect to the mean levels in the 3 sec before the onset of the first noise stimulus.

Ambulatory Monitoring. HRLs were calculated for the 5-min sitting baseline in the clinic and for as much of the BAT course as the subject completed. Other variables were maximum and minimum HRLs during the BAT; mean, maximum, and minimum anxiety ratings during the BAT; number of stations reached; and mean walking speed.

Clinical Variables. Seven psychological variables were selected for statistical purposes as representative a priori of different aspect of the clinical psychological condition of the subject: the Zung Depression Inventory score, the anxiety score from the SCL-90, the agoraphobia score from the Fear Questionnaire, frequency of panic attacks per week based on diary information, observed number of stations reached in the shopping center test walk (Behavioral Approach Test or BAT), and state and trait scores of the State-Trait Anxiety Scale. To these seven variables was added age, to give a total of eight clinical variables.

Statistical Methods. Comparisons between the two groups were made using statistical tests appropriate to the number of measurements within a paradigm. Multiple measurements were subjected to repeated measures Analysis of Variance, with its statistical significance adjusted according to the Greenhouse-Geisser correction or by comparisons of slopes of regression lines. Analysis of Covariance was carried out only when there were no significant group differences in the slopes of the regression lines. Following the recommendations of Venables and Christie (1980), SCL and SCR were log-transformed prior to statistical analysis, whereas HRL and HRR were not. NSF, number of SCRs, number of trials to habituation, and certain SCR magnitude measures were analyzed using nonparametric statistics. Three patients were omitted from the HR and HRR analysis because they were receiving beta blockers for hypertension or other cardiac complaints.

Results

Psychological Evaluation

Figure 1 shows the mean SCL-90 scores for the two groups in terms of *t*-score values for a sample of normal women (Derogatis 1977). The control group had scores near the mean, and the agoraphobic group had high scores on all the scales, especially anxiety

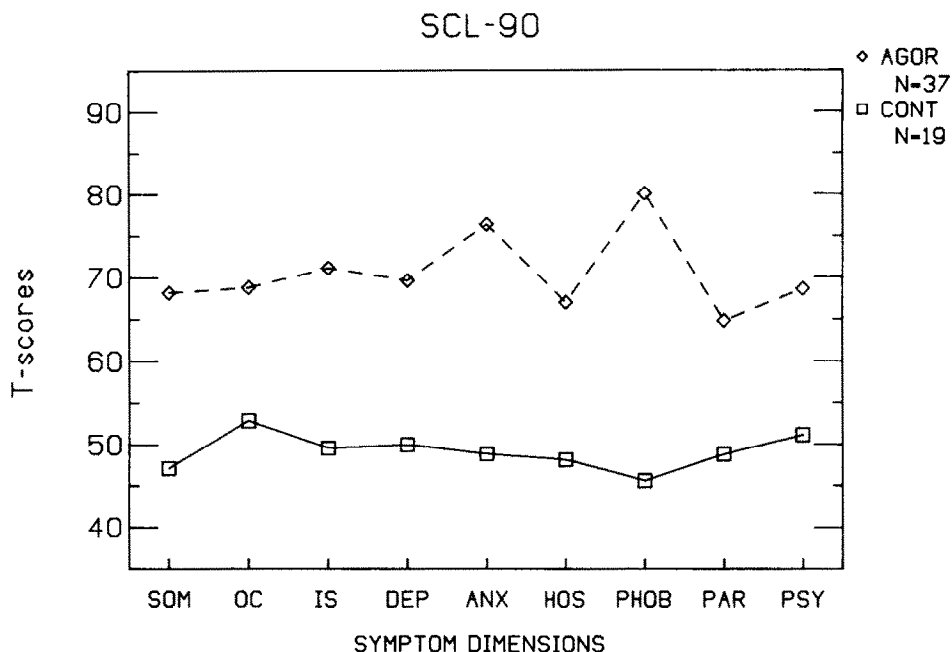


Figure 1. Symptom Checklist-90 (SCL-90) *t*-scores (scaled by a sample of normal women) for agoraphobics (AGOR) and controls (CONT). Individual dimensions are somatization (SOM), obsessive-compulsive (OC), interpersonal sensitivity (IS), depression (DEP), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), and psychoticism (PSY).

and phobia. The agoraphobics had mean Beck scores of 24 and Zung scores of 66 at initial evaluation.

At the time of testing in the laboratory, the mean State-Trait Anxiety Inventory State score was 29.8 for controls and 51.8 for agoraphobics ($p < 0.0005$). Agoraphobics who did not fully comply with our instructions reported levels of state anxiety almost identical to those who did. The strict compliers had a mean score of 50.9, those requiring a companion to sit with them, 49.6, and those having taken antianxiety agents or alcohol within 12 hr, 52.1.

Psychophysiological Testing

Baseline Paradigms. Table 1 presents the statistical analyses of the data illustrated in Figure 2. The skin conductance data were log-transformed before analysis. Agoraphobics had very significantly higher HRLs and SCLs during both baselines. HRLs did not habituate, whereas SCLs did. SCL in baseline 1 showed significant Group \times Time interaction because habituation was faster in controls, as attested to by the *t*-test of linear slopes.

The effect of the noise on SCL during the third minute of baseline 2 is apparent in Figure 2, and together with habituation, explains the main time effect. Subanalyses of variance of data from consecutive minutes (i.e., minute 1 and minute 2, minute 2 and minute 3, etc.) to localize the Group \times Time interaction showed main group and time effects in all pairs, but a Group \times Time interaction only in the first pair. Although not apparent from the untransformed data in Figure 2, this interaction was due to less ha-

Table 1. Statistical Analysis of Baseline Paradigms

Variable	Measure	Statistic	Group	Time	Group \times Time
Baseline 1 paradigm					
HRL	1-min means	ANOVA	^d	NS	NS
	Linear slope	<i>t</i> -test			NS
	1-min means	C vs. A ^d			
SCL	Log 1-min means	ANOVA	^c	^d	^c
	Linear slope	<i>t</i> -test			^b
	Log 1-min means	C vs. A			
NSF	Total number	<i>U</i> -test	^c		
		C vs. A			
	Number/min	Friedman		C ^b	
		5 min		A ^b	
Baseline 2 paradigm (with noise bursts in minute 3)					
HRL	1-min means	ANOVA	^d	NS	NS
SCL	Log 1-min means	ANOVA	^c	^d	^c
	Maximum minute-3 rise	<i>U</i> -test	^b		
		C vs. A			
NSF	Total number	<i>U</i> -test	^b		
		C vs. A			
	Number/min	Friedman		C ^d	
		5 min		A ^d	

^aC, controls; A, agoraphobics.^b $p < 0.05$.^c $p < 0.01$.^d $p < 0.001$.

NS, not significant.

bituation in the agoraphobic than in the control group. The lack of an interaction with group between minute 2 and minute 3 is a sign of no group difference in reactivity, and between minutes 3 and 4, it is a sign of no group difference in recovery. To determine if the reactivity differences would be present if initial SCL was taken into account, an Analysis of Covariance was performed with minute 2 log SCL as the independent variable and minute 3 log SCL minus minute 2 log SCL as the dependent variable, but no group differences emerged. However, maximum SCL rise in minute 3, another measure of skin conductance reactivity to noise, was larger in agoraphobics than in controls ($p < 0.05$). In an Analysis of Covariance with minute 2 log SCL as the independent variable, the adjusted maximum SCL rise in minute 3 no longer differed between groups, showing that the larger SCL rise may be related in some way to tonic SCL differences.

Figure 2 also shows the time course of NSF's in the baseline paradigms for the two groups. In both paradigms, agoraphobics had more NSF's than controls, and both groups showed time effects on Friedman nonparametric Analyses of Variance.

Figure 3 is a scatter plot of 5-min mean HRLs and SCLs in baseline 1 for each subject. The line places all but one control in the left lower region, but only 19 of 34 agoraphobics in the right upper region. (This line was chosen heuristically rather than on the basis of a formal discriminant function procedure. Comparison of the agoraphobics in the two regions on the seven clinical variables and age using *t*-tests gave a significant difference for only the agoraphobia scale ($p < 0.03$), on which more activated patients had higher scores. Four of the patients taking anxiolytics fell in the high activation region and three

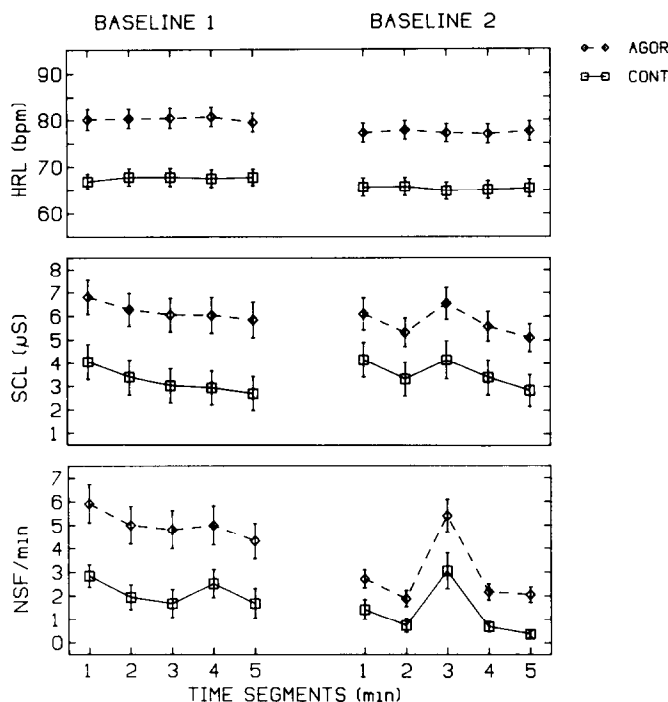


Figure 2. Mean and standard error of heart rate level (HRL) in beats per minute (bpm), skin conductance level (SCL) in microsiemens (μ S), and number of nonspecific fluctuations (NSF) for each 1-min time segment of the two baseline paradigms for agoraphobics (AGOR) and controls (CONT). For HRL, the number (N) of agoraphobics with valid data was 34 for baseline 1 and 32 for baseline 2. For SCL and NSF, the N of agoraphobics with valid data was 37 for baseline 1 and 35 for baseline 2. The N of controls was 19 in all cases.

in the low activation region. Item 39 of the SCL-90 asks if the subject experiences his "heart racing or pounding." The scores of agoraphobics with high and low activation were no different on this item, nor was there any difference on this item for patients having HRLs above and below 80 bpm.

Three heart rate variability measures for baseline 1 differed between agoraphobics and controls. Standard deviations of the 10-sec means and of the 60-sec means were higher in the agoraphobics ($p < 0.03$ and $p < 0.05$, respectively). These measures are significantly correlated with each other in both groups ($r > 0.76$) and were correlated with mean HRL among controls ($r > 0.54$), but not among patients ($r < 0.12$). In addition, the number of reversals per minute was higher in agoraphobics ($p < 0.004$). This measure was uncorrelated with the standard deviation measures in both groups ($r < 0.34$), but correlated substantially with mean HRL ($r > 0.63$). Covarying any of these three variability measures with mean HRL in Analyses of Covariance eliminated the group differences.

Habituation Paradigm. Table 2 presents statistical analyses of data from this paradigm, some of which are presented graphically in Figures 4 and 5. As in the baseline paradigms, both HRL and SCL were significantly higher in the agoraphobics, and SCL, but not HRL,

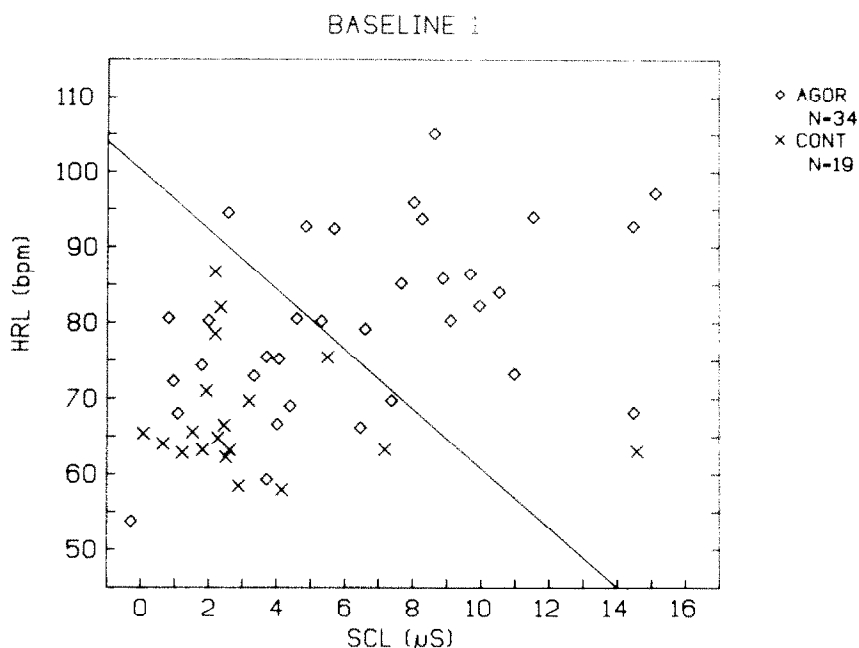


Figure 3. Mean heart rate level (HRL) and skin conductance level (SCL) averaged over the entire 5-min baseline 1 paradigm for individual agoraphobics (AGOR) and controls (CONT) from whom valid data are available. The negatively sloped line is the one that best separates the two groups.

showed habituation effects that had steeper slopes for controls than agoraphobics. For both groups, the total variance explained by linear trend over stimulus number (1–16) was slightly greater for log SCL than for raw SCL, thus justifying our following the usual convention of log transforming SCL in computing these slopes. The same calculations for HRL indicated no advantage for log transformation, and the HRLs were left untransformed.

HRRs to the first stimulus, to stimuli 2–16 averaged in groups of 3, and to stimuli 16–19 were all quite variable, both within and between subjects. None of the three measurements yielded significant effects, except for a time effect for stimuli 16–19 (see Table 2). The HRR to the dishabituating stimulus (17) had larger first and second decelerations (D1 and D2) and less acceleration (A).

For SCRs, the only measure greater for agoraphobics was the total number of SCRs. The magnitude of the first SCR was equal for the two groups, either when tested by U-test or when its log was entered into an Analysis of Covariance with log SCL before the first stimulus as the independent variable. Measures of habituation, such as an analysis of SCR magnitude in blocks of three trials from trial 2 to trial 16, showed time effects, but no group differences. As can be seen in Figure 6, the probability of SCRs fell over the first few trials, so that the average SCR amplitude in the block comprised of trials 2–4 was higher than in other blocks. Two other SCR habituation measures failing to distinguish between groups were number of trials to habituation and the slope of the log magnitude change over trials. In terms of number of trials to habituation, 12% of agoraphobics and 21% of controls were nonresponders (gave zero responses to the first three

Table 2. Statistical Analysis of the Habituation Paradigm

Variable	Trials	Block size	Measure	Statistic	Group	Time	Group × Time
HRL	1-16	1	Prestimulus 2-sec mean	ANOVA	^d	NS	NS
	1-16	1	As above	<i>t</i> -test			NS
			Linear slope	C vs. A ^a			
HRR	1	1	D1	<i>t</i> -test	NS		
				C vs. A			
			A		NS		
			D2		NS		
	2-16	3	D1	ANOVA	NS	NS	NS
			A		NS	NS	NS
			D2		NS	NS	NS
	16-19	1	D1	ANOVA	NS	^c	NS
			A		NS	^c	NS
			D2		NS	^c	NS
SCL	1-16	1	Prestimulus log 0.5-sec mean	ANOVA	^d	^d	^d
	1-16	1	As above	<i>t</i> -test			^c
			Linear slope	C vs. A			
SCR	1	1	Magnitude	<i>U</i> -test	NS		
	2-16	3	Log magnitude	ANOVA	NS	^d	NS
	16-19	1	Magnitude	Friedman		C: NS A: NS	
	17	1	Magnitude	<i>U</i> -test	NS		
	1-19	1	N of SCRs	<i>U</i> -test	^b		
	1-16	1	Trials to habituation	<i>U</i> -test	NS		
	2-3 × 0	1	Log magnitude	<i>t</i> -test			NS
	SCR (max 13)		Linear slope	C vs. A			

^aC, controls; A, agoraphobics.^b*p* < 0.05.^c*p* < 0.01.^d*p* < 0.001.

NS, not significant.

trials), and 15% of agoraphobics and 5% of controls were nonhabitutors. Group differences were not significant by chi-square for either category. Excluding nonresponders, the mean number of trials to habituation was 6.5 ± 4.1 for agoraphobics and 4.4 ± 3.8 for controls. Adjustment of the slope parameter *b* by covarying it with the y-intercept *a* (from the linear regression equation $y = a + bx$) did not produce a significant group effect in an Analysis of Covariance. Table 3 presents the results of analyses of additional SCR variables. No significant group differences appeared among them.

Intensities Paradigm. Table 4 presents statistical analyses of data from this paradigm. HRL showed strong group and weak time effects, due to the agoraphobics having higher HRLs than controls and to both groups showing a decrease in HRL over time. SCL showed group, intensity, and time effects and Group × Time and Time × Intensity interactions. The Group and Group × Time effects were because agoraphobics had higher

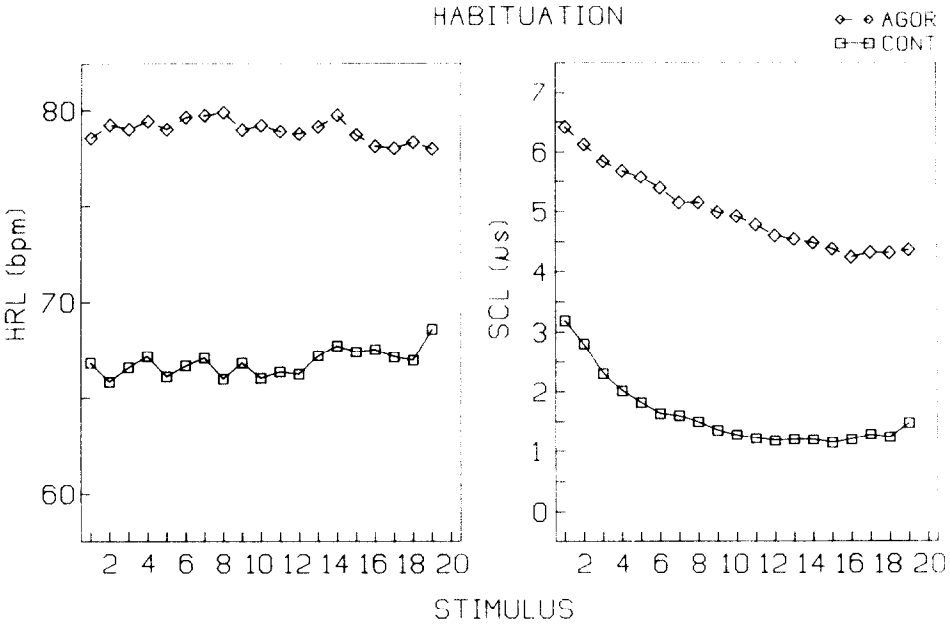
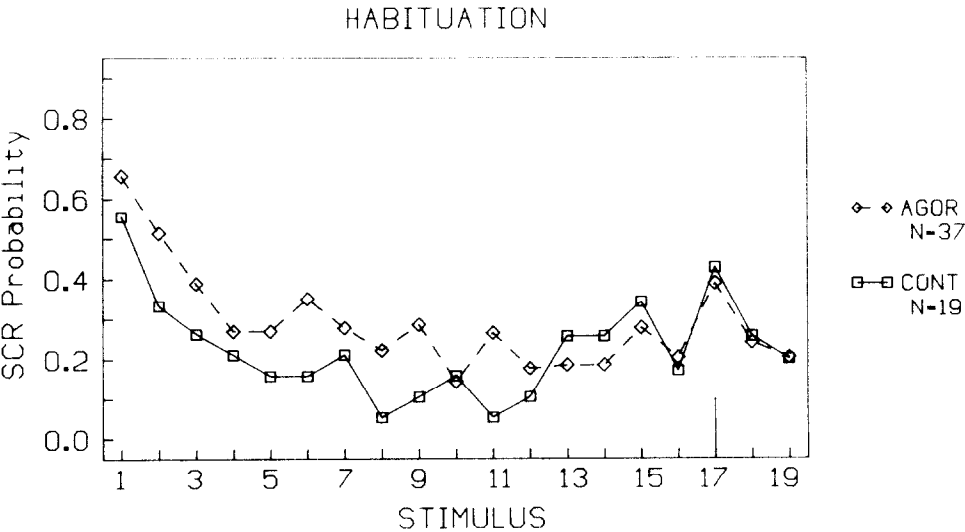


Figure 4. Mean heart rate level (HRL) and skin conductance level (SCL) before each stimulus of the habituation paradigm for agoraphobics (AGOR) and controls (CONT). Nineteen controls had valid data for HRL and 17 controls for SCL. Thirty-one agoraphobics had valid data for HRL and 31 for SCL.

Figure 5. Skin conductance response (SCR) probability for each stimulus of the habituation paradigm for agoraphobics (AGOR) and controls (CONT). Stimulus 17 is different from the other stimuli.



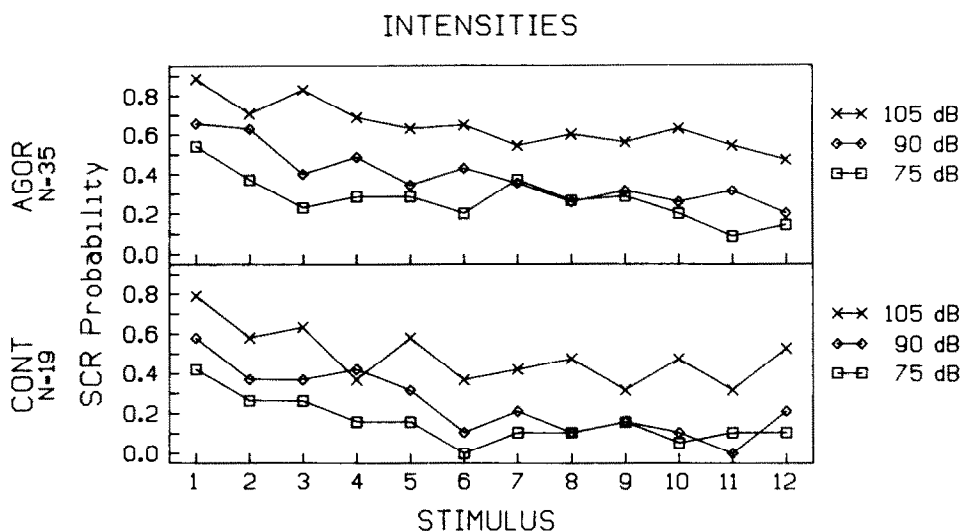


Figure 6. Skin conductance response (SCR) probability for each stimulus of the intensities paradigm for agoraphobics (AGOR) and controls (CONT). The probabilities are shown separately for each of the three noise-pip intensities: 105, 90, and 75 dB.

SCL levels and habituated more slowly. The intensity effects were a consequence of higher intensity stimuli being preceded by lower SCLs. As stimuli were randomized in successive permutations of the three intensities, a higher intensity was more likely to be preceded by a lower intensity and vice versa. The larger SCRs to higher intensity stimuli apparently resulted in higher SCLs that persisted to the end of the ISI. The SCL Time \times Intensity effect was due to an equalizing of SCLs with time, which entailed greater decreases of the higher SCLs preceding lower intensity stimuli. The probability of SCRs tended to be higher for higher intensity and earlier stimuli, and higher in agoraphobics than in controls, as illustrated in Figure 6. As detailed in Table 4, SCR magnitude did not differ significantly between groups, but declined with time and showed

Table 3. Additional SCR Variables from the Habituation Paradigm

Variable	Trials	Controls	Agoraphobics	Unit	Transform	Significance level (<i>t</i> -test)
Amplitude	1	1.08	1.24	μ S	Log	NS
	2-16	0.36	0.31			NS
Latency	1	2.11	1.85	sec		NS
	2-16	2.32	2.35			NS
Rise time	1	1.66	1.76	sec		NS
	2-16	1.76	1.61			NS
One-quarter recovery	1	1.18	1.07	sec		NS
	2-16	1.38	1.03			NS
One-half recovery	1	2.66	2.23	sec		NS
	2-16	2.33	1.98			NS
N SCR/NSF	1-16	3.13	2.49			NS

NS, not significant.

Table 4. Statistical Analysis of the Intensities Paradigm

Variable	Trials	Block size	Measure	Statistic	G	I	T	G×I	G×T	T×I	G×I×T
HRL	1-12 × 3 I	4	Prestimulus 2-sec mean	ANOVA	·	NS	^a	NS	NS	NS	NS
HRR	1-12 × 3 I	4	D1	ANOVA	NS	NS	^a	NS	NS	NS	NS
			A		NS	NS	NS	NS	NS	NS	NS
			D2		NS	NS	NS	NS	^a	NS	NS
SCL	1-12 × 3 I	4	Prestimulus Log 0.5-sec mean	ANOVA	·	·	·	NS	^b	^a	NS
SCR	1-12 × 3 I	4	Log magnitude	ANOVA	NS	·	·	NS	NS	·	NS
	1-12 × 3 I	1	N of SCRs	U-test	NS	105 dB					
					^a	90 dB					
					^a	75 dB					
	1-12 × 3 I	1	N of SCRs	Friedman		C ^c					
						A ^c					

C, controls; A, agoraphobics; G, group; I, intensity; T, time.

^a*p* < 0.05.

^b*p* < 0.01.

^c*p* < 0.001.

NS, not significant.

the intensity effect mentioned. Although the magnitude measures did not yield Group or Group × Time effects, nonparametric tests of the number of SCRs detected a group effect that was weaker for the most intense stimuli. Two significant HRR effects were noted in spite of the low signal-to-noise ratio of these responses: D1 tended to decrease over the first two blocks for both groups, whereas A1 had a tendency to decrease over time in agoraphobics and increase over time in controls.

Ambulatory Monitoring. Table 5 summarizes the ambulatory data. Only 2 agoraphobics reached all 12 stations of the BAT. Subjective anxiety during the BAT was much greater in patients than controls. All HRLs, even the sitting ones, were higher in the

Table 5. Behavior Approach Test (BAT) Measures: Means (Standard Deviations)

Variable	Controls	Agoraphobics	Significance level (<i>t</i> -test)
Stations reached (0-12)	12.0 (0.0)	4.5 (3.4)	<i>p</i> < 0.001
Subjective anxiety (0-10)			
Mean	0.1 (0.2)	5.4 (2.0)	<i>p</i> < 0.001
Maximum	0.2 (0.5)	7.1 (2.2)	<i>p</i> < 0.001
Minimum	0.1 (0.2)	3.7 (2.9)	<i>p</i> < 0.001
Walking speed (m/min)	71 (8)	59 (20)	<i>p</i> < 0.01
Sitting heart rate level (bpm)	78 (10)	92 (15)	<i>p</i> < 0.01
Walking heart rate level (bpm)			
Mean	97 (13)	113 (12)	<i>p</i> < 0.001
Maximum	104 (13)	121 (11)	<i>p</i> < 0.001
Minimum	84 (16)	103 (14)	<i>p</i> < 0.001

patients than in the controls. More problematic is whether patients exhibited more HRL reactivity to the BAT than did controls. The differences between sitting and BAT HRLs are almost equal between the groups. For example, for the mean BAT HRL, this difference is 19 bpm for controls and 21 bpm for agoraphobics. This lack of difference in increase is demonstrated by Analyses of Variance of sitting and walking HRL (done separately for mean, maximum, and minimum HRL) that show highly significant group effects ($p < 0.001$ in each case), but no Group \times Situation (sitting/BAT) interactions. However, Analyses of Covariance performed using the sitting HRL as covariate show that adjusted mean, maximum, and minimum HRL are higher for patients ($p < 0.05$ for mean and maximum and $p < 0.01$ for minimum). The higher BAT HRLs in the patients could not be because patients walked faster: in fact, they walked significantly slower. Analyses of covariance with walking speed as covariate did not increase the significance of the group HRL differences because of the poor correlation between walking speed and HRL. These analyses were repeated with differences between walking HRLs and sitting HRL as dependent variables, but no significant group effects emerged.

Relationships of Variables

Twenty physiological variables that differed significantly between groups were used in a step-wise discriminant analysis to test their independence in classifying subjects. Log SCL during habituation was selected first, and then HRL during baseline 2. At that point, all F s-to-enter were reduced below 3, demonstrating the statistical redundancy of most variables. At step two, 16 of 17 controls and 22 of 27 agoraphobics were correctly classified (these were subjects with complete data on all the variables entered). Thus, the errors in all but one case were due to agoraphobics being misclassified as controls.

Eleven of the 18 physiological variables were selected as representative examples of each type of measurement to form a reduced subset for correlational analyses. It is apparent from Table 6 that heart rate and skin conductance variables tend to form separate clusters. A few correlations between the clinical and the physiological variables were significant. Besides the ones with heart rate variables listed in Table 6, there were a few correlations between clinical and skin conductance variables less than ± 0.40 , but still significant at $p < 0.05$: panic attack frequency with log SCL during baseline 1 (-0.33) and during habituation (-0.35), and number of SCRs during habituation (-0.34). In patients, but not controls, there are significant correlations between age and log SCL during baseline 1 (-0.30) and during habituation (0.32). Neither group had significant correlations between state anxiety in the laboratory and physiological measures.

Compliant and Noncompliant Agoraphobics

Comparisons of compliant and noncompliant subgroups of agoraphobics on the 11 physiological variables selected for correlational analysis gave contradictory indications as to whether agoraphobics who required a companion or who took drugs or alcohol were more or less activated than compliant agoraphobics. HRLs tended to be higher for noncompliant groups, significantly so for the antianxiety drug and alcohol group during baselines 1 and 2 ($p < 0.05$ for each baseline). However, skin conductance variables tended toward lower activation, significantly so for the antianxiety drug and alcohol group on log SCL during habituation ($p < 0.05$). On clinical variables, compliant and noncompliant groups were the same.

Table 6. Correlations ($\times 100$) between Selected Variables

	Controls									
Variable	1	2	3	4	5	6	7	8	9	10
1. Log SCL-B1										
2. Log SCL-H	90									
3. Slope SCL-B1	48	47								
4. NSF-B1										
5. NR-H	80	88	44							
6. HRL-B1										
7. HRL-B2						96				
8. HRVR-B1					-45	63	50			
9. HRV10-B1						54	57			
10. HRL-A1										
11. HRL-A2										

	Agoraphobics											
Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. Log SCL-B1												
2. Log SCL-H	96											
3. Slope SCL-B1	38	47										
4. NSF-B1	73	78	48									
5. NR-H	55	60		66								
6. HRL-B1												
7. HRL-B2						95						
8. HRVR-B1						82	84					
9. HRV10-B1												
10. HRL-A1						68	71	59				
11. HRL-A2						51	61	43		72		
12. Agor						47	42			51	51	
13. PA frequency										-48		-41

Only correlations greater than or equal to 0.40 (all significant at $p < 0.05$) are listed.

SCL, skin conductance level; NSF, number of nonspecific fluctuations; NR, number of skin conductance responses; HRL, heart rate level; HRVR, heart rate variability based on reversals; HRV10, heart rate variability based on 10-sec epochs.

B1, baseline 1; B2, baseline 2; H, habituation; A1, ambulatory sitting mean before walk; A2, ambulatory mean during walk.

Agor, agoraphobia score on Fear Questionnaire; PA, panic attack.

Discussion

The prediction that our agoraphobic patients would have higher tonic levels of activation than controls was strongly supported: agoraphobics had higher HRLs and SCLs during all four paradigms, and their HRLs were elevated before and during the BAT walk. However, contrary to prediction, reactivity measures showed weak and inconsistent differences between groups regardless of the type of stimulus. The magnitudes of the SCR and the HRR to the first orienting stimulus and to the dishabituating stimulus of the habituation paradigm were the same in both groups. Including as part of reactivity the rate of habituation of phasic responses, the number of trials to habituation and magnitude slope of the SCR orienting response in the habituation paradigm were equal in the two groups, though the total number of SCRs in the habituation paradigm, and the total

number of SCRs to 90-dB or 75-dB stimuli in the intensity paradigm, were slightly larger for patients than for controls. The number of SCRs to the most startling (105-dB) stimulus was equal for both groups. The magnitude of the maximum SCR to the series of aversive 90-dB noise bursts in baseline 2 was larger in the patients, but the SCL elevation for the minute when bursts were given was the same. Thus, the evidence for higher SCR reactivity in agoraphobics is equivocal at best, and at worst, may be solely an artifact of NSFs falling within our liberal poststimulus detection range (Levinson and Edelberg 1985; Levinson et al. 1985). As agoraphobics had more NSFs than controls, this artifact would bias SCR measures toward higher values in agoraphobics. Finally, the most surprising example of equal reactivity in the two groups was the equal amount of HRL elevation from sitting in the clinic to walking in the shopping mall, a phobic stimulus for all the agoraphobics, but for none of the controls. Of course, as equality of reactivity is being inferred from instances of statistical insignificance, larger numbers of controls or patients might result in additional examples of differential reactivity. However, the size and importance of such examples would probably be small.

Another kind of habituation—decline in tonic levels over time—may be related more to getting used to the total situation than to reactivity to momentary stimuli. Decline in SCL was slower for patients in all four paradigms, whereas HRLs were relatively stable for both groups.

Recovery of SCRs to individual stimuli of the habituation paradigm and of SCL in the fourth and fifth minute of baseline 2 after the noise bursts in the third minute did not differ between groups. We had predicted slower SCR recovery for patients, which is in keeping with some data of Chattopadhyay et al. (1975). However, the observations of Bundy and Fitzgerald (1975) in normal subjects imply that the frequent NSFs among the patients could have sped recovery. In any case, we found all temporal SCR parameters to be equal between groups.

Stimulus-independent variability was greater for patients in baselines 1 and 2, in that their NSFs were more numerous. Also, several measures of heart rate variability were higher for patients in baseline 1. Increased variability measures simply may reflect greater tonic anxiety, or alternatively, may indicate paroxysmal increases in autonomic activation underlying panic attacks.

Our results have certain features in common with those of Lader and Wing (1964, 1966). Their anxious patients had tonically higher HRLs and SCLs during a habituation paradigm and a slower decline in SCL. However, in their study, SCR amplitudes after the SCR to the first stimulus habituated significantly more rapidly for controls than for patients, whereas our measures of SCR habituation were the same between groups. It is possible that this discrepancy between their results and ours is due to patient selection. Their patients all suffered from somatic symptoms of anxiety in a free-floating or situational form, sometimes accompanied by depression. Although the majority had panic attacks, less than half had agoraphobic symptoms. However, in a second study (Lader 1967), a pure group of agoraphobics showed an even slower SCR habituation rate than anxious patients without agoraphobia.

A more likely reason for the discrepancy in habituation findings is that Lader gave 100-dB 1-sec tones, an intensity likely to elicit "defense" rather than orienting responses (Graham 1979), whereas we gave 75-dB tones in our habituation paradigm. Our results are consistent with other studies using lower intensity or mixed intensity tones (Tan 1964; Hart 1974), whereas the Lader results are consistent with Raskin (1975) and Horvath and Meares (1979), who used 100-dB tones. A relationship between habituation differences

between anxious patients and controls and tone intensity was first pointed out by Öhman (1981). Our intensities and baseline 2 paradigms presented louder stimuli than our habituation paradigm, but they were not equivalent to Lader's: the 105-dB noise bursts in our intensity paradigm lasted only 50-msec, which gave them a startling, but not particularly intense, quality, and the 90-dB 1-sec noise stimuli in baseline 2 were given at 3-sec intervals.

If positive feedback occurs, as postulated by Lader and Mathews (1968), it must occur only when subjects encounter very powerful stimuli. Even repeated 90-dB 1-sec noise stimuli given at short intervals raised SCL almost exactly equally in patients and controls, although SCL was higher in the patients throughout stimulation. That their higher SCLs did not slow SCR habituation is congruent with their subjective reports, which suggest that anxiety can result in less, rather than more, reactivity to milder stimuli. When asked if they found the stimuli disruptive, patients often said that they were so concerned with their environment or bodily sensations that they hardly noticed them. Distraction can reduce SCRs and speed habituation (Iacono and Lykken 1983), although this is not always the case (Becker and Shapiro 1980; Stenfert Kroese and Siddle 1983; Roth et al. 1984).

The fact that HRL did not rise more in patients than in controls when exposed to the continuous, psychologically intense stimulus of the shopping mall is both contrary to a positive feedback model, as the patients began the mall walk with higher HRLs, and to the elementary assumption that phobic stimuli will induce more autonomic activation in people who are afraid of them. We are left with post-hoc explanations for the ambulatory heart rate findings: anticipatory anxiety during the sitting period may have been as strong as phobic anxiety during walking and may have raised HLR levels equally at both times; the exercise effect on walking HRL may have preempted the anxiety effect; or the higher tonic heart rates of the patients may have downscaled absolute HR reactivity to the mall walk through the operation of the Law of Initial Values. Significant group differences emerging when walking HRLs were adjusted for sitting HRLs using Analysis of Covariance give some support to the last explanation, but it should be borne in mind that these group differences represent only a prediction of a hypothetical state of affairs, namely, that control walking HRLs would have been lower than those of patients if control sitting HRLs had been as high as those of patients. The results of the Analysis of Covariance cannot negate the fact that taking reactivity in its simplest meaning, the reactivity of patients and controls was equal (for discussions of the problems using covariance adjustments in this context, see Levey 1980, pp 617-624, and Myrtek 1984, pp 129-134.) Other investigators not only have failed to find greater heart rate reactivity in anxious patients, but actually have found less. Kelly et al. (1968) reported that anxious patients had higher HRL baselines, but smaller increases to the stress of mental arithmetic. Analysis of Covariance confirmed the smaller increases (Kelly et al. 1970).

Our results give little support to Gray's neuropsychological theory of anxiety, which postulates that anxious people have a more responsive "behavioral inhibition system" (Gray 1982a), one of the major inputs of which is novel, orienting response-producing stimuli. His theory could be vindicated if we could demonstrate that the more frequent NSFs among agoraphobics are orienting responses to internal or external stimuli that are more compelling than the sound stimuli presented. Another possibility is that panic anxiety of our patients is physiologically different from the kind of anxiety that Gray is able to explain (Klein 1981; Gray 1982b).

The overall pattern of differences between patients and controls suggests that the patients were higher on a general autonomic activation or arousal factor that included

both electrodermal and heart rate measures. However, as usual (for review, see Fowles 1982), correlations showed strong interrelationships within response systems, but weak interrelationships between systems. The relative independence of skin conductance and heart rate are most obvious in the time course of the variables: HRL declined little during the laboratory session, whereas SCL did. Such dissociations complicate, but do not invalidate, the concept of activation, as, for example, the specific regulatory functions of the autonomic nervous system take priority over their registration of general arousal and distort that registration (Venables 1984).

In spite of large group differences in autonomic variables, individual agoraphobics had values that were the same as controls. These agoraphobics did not report themselves at the time of testing to be less anxious or more depressed than the other patients, depression being a possible cause of reduced SCL (Iacono et al. 1983; Ward et al. 1983). These exceptions were one reason for the lack of significant correlations between state anxiety and autonomic variables. There are a number of possible reasons for patients reporting anxiety symptoms without showing physiological signs of anxiety: their self-reports may be erroneous, with the patients misperceiving or exaggerating their anxiety level; or their anxiety may be of a cognitive or worrying variety that is not accompanied by autonomic activation; or learned anxiety symptoms may linger on after the hypothetical disease process producing autonomic activation has ebbed; or activation may have become decoupled from the disease process or from psychic anxiety by the operation of an additional factor. Depersonalization, for example, can abruptly reduce heart rate and skin conductance in an anxious person (Lader 1975, pp 192-193). However, most likely is that these patients manifest control values on autonomic measures because of idiosyncratic individual differences unrelated to psychological state or trait or to disease process. Finding a way to take these differences into account is an important task for psychophysiology (for a recent discussion of "individual-specific response patterns," see Myrtek 1984, pp 198-201).

Although agoraphobics as a group are autonomically activated in the laboratory, patients with "specific phobias" are not (Lader 1967). This does not entail that agoraphobia is basically different from other phobias psychologically or biologically. The activation differences may occur simply because the laboratory situation itself is a likely phobic stimulus for agoraphobics, but not for most simple phobics. Agoraphobics are commonly claustrophobic, afraid of being separated from their supporting companion, and uneasy at being constrained by recording leads attached to their bodies, whereas simple phobics may be undisturbed by the isolating, constraining features of the laboratory if they do not expect to encounter their specific phobic stimulus there. If that phobic stimulus is later introduced, they react autonomically, like agoraphobics. For example, simple phobics react with heart rate acceleration when exposed in reality to their feared object (Sartory et al. 1977) or to pictures of it (for a review, see Sartory 1983). Our highest positive correlations between self-rating scales and physiological variables in the laboratory were between the Agoraphobia Scale and HRL, which is consistent with this interpretation. Not only was the laboratory a likely phobic situation, but to reach our laboratory, the patients had to leave their homes and drive through city streets, which for many was frightening.

However, if further experiments show that the activation of agoraphobics remains high in nonthreatening settings, the plausibility of the alternative explanation—that agoraphobics suffer from an altered internal state relatively uninfluenced by external events—would be strengthened. Such an alternative would be consistent with the lack of reactivity

differences between groups and with the possibility that spontaneous heart rate variability and NSFs are indications of activating internal events.

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