Learning to Have Psychosomatic Complaints: Conditioning of Respiratory Behavior and Somatic Complaints in Psychosomatic Patients

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Objective: Assuming a subjective similarity between the experience of a hyperventilation episode and inhaling CO_2-enriched air, we tested whether a respiratory challenge in association with a particular stimulus could result in altered respiratory behavior and associated somatic complaints upon presenting the stimulus only.

Method: Psychosomatic patients (N = 28) reporting hyperventilation complaints participated in a differential conditioning paradigm using odors with a positive or negative valence as conditioned stimuli (CS+ or CS−) and 7.4% CO_2-enriched air as the unconditioned stimulus (US). Three CS+ and three CS− acquisition trials were run. During the test phase, two CS+- and two CS−-only trials were run, followed by two new test odors (with a positive or negative valence). Respiratory frequency, tidal volume, end-tidal fractional concentration of CO_2, and heart rate were measured throughout the experiment. Somatic complaints were registered after each trial.

Results: We observed a) increased respiratory frequency and an elevated level of somatic complaints upon presenting the CS+ only; b) a selective association effect: conditioning was only apparent with the negatively valenced CS+ odor; (c) no generalization of respiratory responses and complaints to the new odors; (d) no conditioning effect on dummy complaints that are usually not reported when inhaling CO_2; (e) in exploratory comparisons with normal subjects, stronger conditioning effects on typical hyperventilation complaints in patients, and, in female subjects, on respiratory frequency.

Conclusion: Respiratory responses and psychosomatic complaints can be elicited by conditioned stimuli in a highly specific way. The findings are relevant for disorders in which respiratory abnormalities and/or psychosomatic complaints may play a role and for multiple chemical sensitivity.

Key words: *conditioning, hyperventilation, panic, odors, psychosomatic complaints, multiple chemical sensitivity.*

INTRODUCTION

Because psychologic stress may evoke hyperventilation and hypocapnia (reduced arterial carbon dioxide level), which may in turn provoke somatic and psychologic symptoms (1, 2), hyperventilation has been suggested as a mechanism mediating between stress and psychosomatic complaints both in normal subjects (3) and in patients (4, 5). Ley (5), for example, hypothesized that hyperventilatory hypocapnia may cause symptoms such as dyspnea and tachycardia and trigger panic attacks. Klein (6) and Papp et al. (7) suggested that panic patients hyperventilate as a consequence of a hypersensitive respiratory control mechanism, which is initially triggered by a central buildup of CO_2. However, recent evidence suggests that hyperventilation may be grossly overstated as a mechanism that produces these complaints, because similar complaints may be present in the absence of a reduced P_{CO_2} level (8–11). In addition, normal subjects who score themselves higher on questionnaires measuring negative affective states (12) and subjects reporting more psychosomatic symptoms (3, 13) tend to have lower P_{CO_2} levels. However, a recent study (14) showed that most of the variance (33%) in psychosomatic complaints was explained by psychologic variables, whereas the end-tidal P_{CO_2} level added only 4% of explained variance. Therefore, psychologic processes such as hypervigilance in symptom perception and a negativistic interpretative bias (15, 16) have been suggested as predominant explanatory mechanisms.

The physiologic and psychologic mechanisms involved in psychosomatic complaints are of course not mutually exclusive. For example, occurrences of hyperventilation may be considered learning episodes in which subjects increasingly learn to attend to and anxiously interpret (normal) somatic variations, which may produce complaints and cause altered breathing as well. Eventually, the relation-

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ship between hyperventilation and somatic complaints may become reversed over time within an individual. In other words, the complexities of the relationship between respiratory physiologic challenges and psychosomatic complaints may be better understood in a dynamic perspective.

In a previous experiment, we investigated whether subjects could learn to breathe differently and to experience psychosomatic complaints as a consequence of respiratory challenges, and we analyzed the relationship between respiratory behavior and somatic complaints in normal subjects (17). Two odors served as conditioned stimuli (CSs), and CO_2-enriched air served as the unconditioned stimulus (US) in a differential respiratory conditioning paradigm: one conditioned stimulus was simultaneously presented with the CO_2 (CS+); the other, with regular air (CS−). During subsequent presentations of the CS+ only, we observed a conditioned increase both in respiratory frequency and in somatic complaints, although increased breathing did not produce hypocapnia. The conditioning effect was confined to the foul-smelling ammonia serving as the CS+ and did not appear when fresh-smelling niaouli (a eucalyptus oil mixture) was the CS+. Furthermore, the conditioned increase in somatic complaints was predicted by increases in somatic responses and not by individual differences in negative affect. However, there was a poor matching between the type of complaints and the type of somatic responses that served as the best predictor, suggesting that somatic responsivity is important as a basis for complaints, but not through accurate perception of the somatic responses.

The present study aimed to replicate our conditioning effects on respiratory behavior and somatic complaints (17) in a sample of psychosomatic patients presenting hyperventilation complaints. A number of additional features were included in this study. First, to test the specificity or generalization of the learning effect, we added two new odors (with a positive and a negative valence, respectively) in the test phase. Second, a set of dummy complaints that usually are not reported when breathing CO_2 was added to the subjective complaint list. This set served to test whether the complaints triggered by the CS+ odor were specifically related to the complaints during acquisition, or whether the CS+ sensitized subjects to report complaints unrelated to the CO_2 challenge as well. Third, the selective association effect observed in the previous study suggested that simple cognitive awareness of the contingencies between the CSs and the US involved was probably not sufficient to produce conditioned respiratory responses and complaints. However, cognitive awareness was not explicitly tested. Such a test was included in the present study. Furthermore, because women seem to be more vulnerable than men to hyperventilation (18–20) and tend to be more prone to experience complaints (21), we included gender as a variable.

In addition, a replication with psychosomatic patients reporting hyperventilation complaints allowed an exploration of some functional differences between patients and normal subjects. First, the physiologic response to a CO_2 challenge as US may be stronger in patients than in normal subjects because of a hypersensitive respiratory control mechanism (7, 6, 22, 23) or because the subjective impact of the challenge may be experienced as more negatively arousing (24–26). Second, patients with hyperventilation may be excessively attentive to typical respiratory complaints. Attentional direction may therefore prime both reporting more complaints of that type during acquisition and subsequently facilitate their conditioning, even without physiologic differences during either the acquisition or test phase. To explore some of these issues, we compared the present patient sample with the normal one from the Van den Bergh et al. (17) study, which used the same paradigm.

METHOD

Subjects

Twenty-eight psychosomatic patients (mean age 36, ranging between 20 and 57 years, 14 male subjects) voluntarily participated in the study after an informed consent was collected. They were referred to the pulmonary consultation unit of the university hospital because of complaints suspected of being caused by hyperventilation, after other somatic conditions had been excluded. Inclusion criteria were a) the patients' recognition of their major complaints after a hyperventilation provocation test (27) and b) scoring positive on the Nijmegen Questionnaire for Hyperventilation Syndrome (28), a diagnostic tool comprising 16 complaints to diagnose hyperventilation. The sensitivity of this instrument is 91% and the specificity is 95%. Twenty-three subjects were classified as hyperventilation patients, and five were classified as likely hyperventilators, because of fulfilling only one of the two criteria. According to the Diagnostic Interview Schedule (DSM-III-R) classification, the sample included patients with anxiety disorder ($N = 7$), somatization disorder ($N = 7$), and mood disorder ($N = 3$). Six patients qualified for both anxiety and mood disorder, three for both somatization and mood disorder, and two for both anxiety and somatization disorder.

Materials

Subjective Measures. Subjective complaints were measured using a list of 16 complaints (see Table 1 in the Results section).

TABLE 1. Mean Scores per Complaint, per Set of Complaints and Total Mean Scores during Acquisition (CO_2 and Air) and Test with Ammonia or Niaouli as CS+

	Acquisition		Test				
			Ammonia CS+		Niaouli CS+		
	CO_2	Air	CS+	CS−	CS+	CS−	
1. Arousal							
a. Tension	2.32	1.65	1.78	1.57	1.35	1.21	
b. Anxious feeling	2.16	1.39	1.60	1.46	1.21	1.21	
c. Feelings of panicking	2.09	1.40	1.82	1.46	1.17	1.17	
Mean sum	6.57	4.44[a]	5.20	4.49	3.73	3.59	NS
2. Respiration							
a. Fast breathing	3.22	1.66	2.07	1.53	1.60	1.53	
b. Smothering sensations	2.98	1.53	2.14	1.25	1.64	1.39	
c. Chest tightness	2.01	1.40	1.67	1.28	1.42	1.32	
d. Feelings of choking	2.47	1.29	1.75	1.17	1.35	1.32	
Mean sum	10.68	4.23[a]	7.63	5.23	6.01	5.56	Cond;[a] Cond x CS+ Odor[b]
3. Cardiac/warmth							
a. Pounding heart	1.90	1.27	1.17	1.10	1.35	1.39	
b. Sweating	2.02	1.44	1.57	1.39	1.25	1.25	
c. Hot flushes (head)	1.90	1.45	1.60	1.60	1.28	1.17	
Mean sum	5.82	4.16[a]	4.34	4.09	3.88	3.81	NS
4. Tingling sensations							
a. Tingling, numbness (extremities)	1.52	1.26	1.25	1.25	1.28	1.22	
b. Tingling, numbness (face)	1.44	1.22	1.25	1.17	1.32	1.28	
Mean sum	2.96	2.48[b]	2.50	2.42	2.60	2.50	NS
5. Unclassified							
a. Lump in throat	1.82	1.38	1.89	1.42	1.35	1.28	
b. Headache	1.69	1.48	1 57	1.42	1 57	1.46	
c. Dizziness	2.32	1.58	1.89	1.50	1.71	1.57	
d. Cold Chills	1.42	1.17	1.14	1.14	1.25	1.17	
Mean sum	7.25	5.61[a]	6.49	5.48	5.88	5.48	Cond[a]
Total mean sum	33.28	20.92[a]	26.16	21.71	22.10	20.94	Cond;[a] Cond x CS+ Odor[b]
6. Dummy							
a. Joint pain	1.32	1.30	1.32	1.32	1.21	1.21	
b. Sleepy feeling	1.58	1.44	1.42	1.53	1.71	1.64	
c. Low back pain	1.23	1.20	1.28	1.28	1.25	1.25	
d. Stuffed nose	1.61	1.55	1.89	1 64	1.35	1.39	
e. Burning eyes	1.44	1.30	1.39	1.28	1.53	1.39	
Mean sum	7.18	6.79[c]	7.30	7.05	7.05	6.88	NS

[a] $p < .005$.
[b] $p < .05$.
[c] $p < .01$.

The items were selected after analysis of published reports using CO_2 inhalation (26, 29, 30) and from the Nijmegen Questionnaire for Hyperventilation Syndrome (28). The complaint list was the same as that in our earlier study (17), where it was shown sensitive to detecting CO_2 inhalation and subsequent conditioning effects. For each of the complaints, a five-point graded answer reflecting intensity could be given to the question, "Did you feel any of these complaints". The categories were: not at all, slightly, medium, strong and very strong (respectively coded as 1, 2, 3, 4, and 5). The total complaint score was the sum of these scores and was treated as a continuous variable (range 16–80). Five subsets of complaints were formed and analyzed separately: a) general arousal, b) respiration, c) cardiac/warmth, d) tingling sensations, and e) unclassified. These subsets were similar to those used by Wientjes and Grossman (14). They are based on factor analysis of a large list of psychosomatic complaints administered to over 500 subjects. In addition, a set of four complaints that are usually not reported for CO_2 inhalation was added as a dummy subset (see Table 1).

Before the start of the experiment, and as a part of the regular diagnostic procedure during consultation, patients completed a Dutch adapted version of, respectively, the State and Trait Anxiety Inventory (STAI) (31, 32). In addition, the Nijmegen Questionnaire for Hyperventilation Syndrome (28) was filled out (see above). During the pause between the acquisition and the test phase, subjects filled out the Miller Behavioral Style Survey (MBSS) (33), in a Dutch adaptation by Van Zuuren and Wolfs (34). The MBSS measures information seeking and blunting behavioral

styles in confrontation with aversive events. It has been validated in threatening laboratory situations and it seems independent from trait anxiety (33).

Apparatus. The CO_2 mixture consisted of 7.4% CO_2, 21% O_2, and 71.6% N_2; the placebo mixture was breathing air of 21% O_2 and 79% N_2. Both gases were contained in standard gas cylinders. After decompression, the gases were first fed into a metereologic balloon and then in a wide vinyl tube ending on a double one-way valve serving as input for a pneumotachograph (Fleisch No. 2, Switzerland) and a mask enclosing the mouth and nose. The subject kept it slightly pressed on the face. A Y-valve could be switched to feed either the breathing air or the CO_2 mixture into the tube.

The one-way valve ensured complete separation of inspired and expired air. Expired air was led outside through an open window to avoid the odors filling the room. During quiet breathing, maximal pressures at the mouth were about 2.5 and 3.2 cm H_2O, respectively, during inspiration and expiration. An infrared CO_2 monitor (Capnograph, Mark II, Godart Bilthoven, The Netherlands) was connected close to the mouthpiece, monitoring the CO_2 pressure continuously during inspiration and expiration. It was calibrated before each experimental session using calibration gas containing 7.45% CO_2. The pneumotachograph and the CO_2 monitor were connected to a Labmaster card and a PC. The volume and CO_2 waveforms were sampled at a sampling rate of 20 Hz. All waveforms were visually inspected off-line to eliminate technical abnormalities and movement artifacts. Specifically designed software was used to extract pauses and irregularities, inspiratory and expiratory time, inspiratory and expiratory volume and fractional concentration of CO_2 per breathing cycle. The heart rate was measured using an electrical plethysmographic sensor attached to the right index finger and the number of peaks during each 2-minute period was calculated.

Air from a separate cylinder was led through one of two aerosol devices at a rate of 1 to 1.5 liters/min to take up an odor and was then fed into the wide tube, upstream from the double one-way valve and the pneumotachograph and close to the mask. The smelling substances were either niaouli (a mixture of volatile oils, containing 65% eucalyptus oil) or a diluted solution of ammonia (0.085%). Both odors were dispersed in a concentration that produced a rather pungent smell but was too low to have any noticeable effects on the breathing pattern itself, as was shown in our previous study with this paradigm (30).[1] Two new odors were introduced at the end of the test phase: a) Ichtyol^R (an ammonium ichtyosulfonate), a darkly colored viscous fluid with a strong, characteristic tarry odor with a negative valence (used in much larger concentrations as a topical anti-infective medication); and b) rose extract, available in regular drugstores and producing a positively valenced odor.

[1]In a 2-minute period, approximately 80 mg and 40 mg of the ammonia solution and niaouli, respectively, were dispersed. For a ventilation of 10 liters/min, the corresponding inhaled quantities are 1:7 mg/m^3/min for ammonia, 2 g/m^3/min for niaouli. Because the smell-air mixture was additionally fed into the system, the 7.4 CO_2-concentration has been slightly diluted, but this was similar for all the subjects.

Procedure

Subjects arrived as outpatients after referral by either their general physician or by specialists because of suspected hyperventilation complaints. They were tested in a standardized diagnostic procedure, involving the Anxiety Disorder Interview Schedule (ADIS-R) interview (35), the completion of a number of questionnaires (see above) and a hyperventilation provocation test. Thereafter, subjects were invited to participate in an additional test for research purposes. Subjects who volunteered to participate were told that: a) the experiment aimed at testing respiratory behavior while the patient breathed different innocuous gases; b) minor complaints such as a little dizziness, headache, and shortness of breath could temporarily appear with some of these gases, but they would disappear quickly after the experimental session; and c) they were allowed to stop the experiment at any moment. The diagnostic procedure and the experiment were separated by approximately 30 minutes.

The subjects were led to the experimental equipment and told that the experiment consisted of two blocks of seven breathing trials, each trial requiring them to breathe for 2 minutes through the mask. After each trial, a pause lasting 3 minutes was scheduled to fill out a questionnaire intended "to check how he/she felt after breathing that specific gas." The subjective complaints questionnaire was then administered. Subjects were told that three different mixtures were to be inhaled, and no further details were given. They were asked to wait for the signal of the experimenter to put the mask on and take it off.

The first trial within each block was a habituation trial: the subject breathed regular air through the mask, without any odor or gas added. Then, six consecutive trials were run. In the acquisition phase, three of them were CS+/US compounds and three were CS−/air compounds. Half of the subjects had ammonia as CS+ and niaouli as CS−, and the other half had the reversed combination. The order of the six trials was counterbalanced across subjects, with the restriction that no more than two consecutive trials could be of the same type. This resulted in 14 possible orders for the combination CS+ (ammonia) and CS− (niaouli). Reversing the combination made up 28 different trial patterns in total. One subject was run per trial pattern, balancing gender within each combination. A pause of half an hour separated acquisition and test. Immediately after the acquisition phase, the odor evaluation and contingency awareness tests were run. Subjects were given a brief puff of each of the two odors. They rated first the affective valence on a −5 to +5 scale after each puff, and after both, they indicated which of the two odors had caused more complaints ("first," "second," or "don't know"). The responses were scored 1 and −1, respectively, for indicating the CS+ and the CS− odor, and 0 for "don't know" answers. Next, the MBSS was filled out. Subjects were then led to a waiting room where they found reading materials and could relax for half an hour between acquisition and test.

The test phase started with telling the subjects that for reasons of experimental control, the tests were done twice. Then, an identical replication of the acquisition phase was run with the exception that a) no CO_2 was added to any of the trials, which was not told to the subject; b) the odors in the last two trials were replaced by Ichtyol and rose, presented in a randomized order (see above); and c) that the same questions regarding affective valence and felt complaints were subsequently also asked regarding Ichtyol and rose.

The subject sat on a chair and the apparatus was placed out of sight. The experimenter manipulated the valves and watched carefully to ensure that the subject's mask remained in place during breathing.

Data Analysis And Design

Physiologic parameters included frequency (f, number of breaths per minute); end-tidal fractional concentration of CO_2, expressed as a percentage ($FETco_2$); tidal volume (V_T); and heart rate in beats per minute (bpm). Analyses were carried out on means per trial for frequency (f), tidal volume (V_T), minute ventilation ($V_E = V_T \times f$), end-tidal fractional concentration of CO_2 ($FETco_2$), and heart rate.

The data of the two habituation trials (one context exposure trial in the acquisition phase and one in the test phase) were analyzed in a CS+ odor (ammonia/niaouli) × gender (male/female) × trial (acquisition/test) design. Analyses of variance (ANOVAs) on the data of the test results had a CS+ odor (ammonia/niaouli) × gender × conditioning (CS+/CS−) × trial (one, two) design, among which the first two were between-subjects variables and the latter two were within-subjects variables. The trials including the new odors were analyzed separately. ANOVAs on the acquisition data included a mixture variable (CO_2/air) replacing conditioning, whereas the trial variable had three levels. Analyses on subjective complaints were done on the total complaint score and on the various subsets of complaints. Heart rate results are mentioned only when significant and meaningful effects appear. Greenhouse-Geisser corrections were used when appropriate. Stepwise multiple-regression analyses with forward inclusion of variables were carried out to analyze the relationship among negative affectivity, MBSS, somatic responses, and complaints. The comparison with the normal subjects from our earlier study (17) was done for both the acquisition and test phase using the respective design as described above, but adding one between-subject variable (status: normal/patient).

RESULTS

Context Exposures

Subjective Complaints. A trial × gender interaction emerged for the total complaints score ($F(1,24) = 7.81$; $p < .05$). Complaint scores decreased in the second context exposure trial but only for female subjects (means for the first and second trial were 23 and 23.7 for male subjects, and 22.8 and 19.8 for female subjects).

Respiratory Behavior. Trial effects were found for V_E ($F(1.24 = 6.85$; $p < .05$) and for $FETco_2$ ($F(1,24) = 11.06$; $p < .005$): the second context trial produced lower values than the first. Also, the heart rate was significantly lower during the context trial at test ($F(1,24) = 11.92$; $p < .005$) (see Table 2). Furthermore, female subjects had overall lower $FETco_2$ ($F(1,24) = 5.49$; $p < .05$). It can be concluded that mainly habituation effects occurred and that conditioning effects during the test cannot be explained by (conditioned) differences in responses to the context.

Mere Odor Effects. As a control on possible effects of the odors themselves on complaints or breathing behavior, exploratory analyses were carried out on the context exposure trial during the acquisition phase and the first acquisition trial of the 14 subjects that started with a CS− trial. Seven of them had ammonia first, seven other subjects had niaouli first, both mixed with regular air. Differential mere odor effects should appear as a trial (context/CS− trial) × odor (ammonia/niaouli) interaction. Neither subjective complaints nor respiratory behavior showed evidence for unconditional odor effects. This replicates the finding with normal subjects (17).

TABLE 2. Respiratory Frequency, Minute Ventilation (Liters/Min) and End-Tidal Fractional Concentration of CO_2 (Means Across Trials)

	f	V_E	$FETco_2$
Context exposure			
Before acquisition	14.5	10.61	4.39
Before test	14.9	9.93	4.21
Acquisition			
Ammonia CS+			
CS+	17.3	16.14	7.01
CS−	15.3	10.84	4.12
Niaouli CS+			
CS+	16.1	15.44	6.97
CS−	15.0	9.92	4.18
Test			
Ammonia CS+			
CS+	16.8	10.57	4.05
CS−	15.0	9.72	4.12
Niaouli CS+			
CS+	14.9	9.22	3.98
CS−	14.7	8.92	3.97

Acquisition

Subjective Complaints. A highly reliable gas mixture main effect appeared ($F(1,24) = 54.14$; $p < .0001$; total complaint means were 33.3 during CO_2 vs. 21 during regular air). This effect was apparent in all the subsets of complaints, including the dummy complaints (F's ranging from 4.9 (dummy) and 6.64 (tingling) to 86.87 (respiration)). A main effect of Trial ($F(1.7,41.8) = 7.88$; $p < .005$) indicated an habituation effect over trial across CO_2 and regular air inhalation.

Respiratory Behavior. Frequency, tidal volume, minute ventilation, and end-tidal fractional concentration of CO_2 were all affected by the inhaled gases (f: $F(1,24) = 6.95$, $p < .02$; V_T: $F(1,24) = 33.07$, $p < .0001$; V_E: $F(1,24) = 44.74$, $p < .00001$; $FETco_2$: $F(1,24) = 1575$, $p < .0001$). Also, heart rate was significantly affected ($F(1,24) = 16.73$; $p < .0005$); means were 80 and 77.5 bpm for CO_2 and regular air, respectively. A significant gender effect emerged for

V_T ($F(1,24) = 7.56$, $p < .05$), and it was marginally significant for V_E ($F(1,24) = 3.78$, $p = .06$). Female subjects breathed less deeply and tended to have lower minute ventilations. Physiologic data are presented in Table 2.

Comparison with Normal Subjects. In general, the response to the respiratory challenge was not stronger in patients than in normal subjects. For $FETco_2$, a status (patients/normal subjects) × mixture interaction emerged ($F(1,48) = 7.51$; $p < .01$), but this reflected a difference between patients and normal subjects when breathing air. For respiratory, unclassified, and tingling complaints, we observed strong main effects of status (respiration: $F(1,48) = 18.34$; $p < .0001$; tingling: $F(1,48) = 15.26$; $p < .0005$; unclassified: $F(1,48) = 12.2$, $p < .005$); regardless of type of inhaled gas, patients had more complaints than normal subjects. However, a status × mixture interaction fell short of statistical significance for respiratory complaints ($p = .10$) and for the unclassified set ($p = .07$): the difference between normal subjects and patients tended to be larger during CO_2 inhalation.

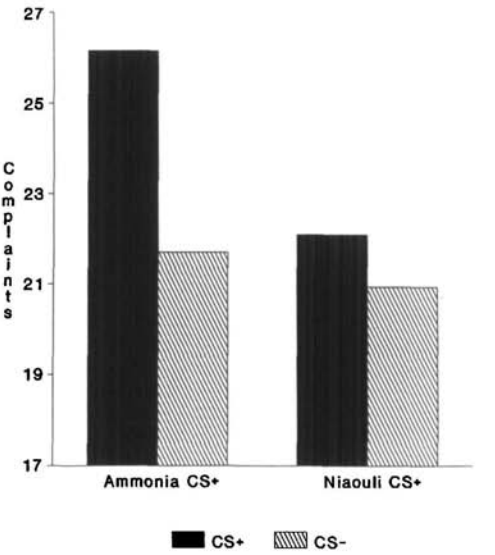

Fig. 1. The conditioning effect on subjective complaints as a function of type of CS+ odor (ammonia or niaouli).

Test

Subjective Complaints. For the total complaint score, a significant conditioning main effect (conditioning: $F(1,24) = 13.27$; $p = .001$) was specified by a conditioning × CS+ odor interaction ($F(1,24) = 4.62$; $p < .05$; see Fig. (1). Simple main-effect analyses showed that, only when ammonia served as CS+, a significant conditioning effect (CS+/CS−) emerged ($F(1, 24) = 12.57$; $p < .001$), but not when niaouli was the CS+ ($F(1,24) = 1.26$; not significant [NS]). Also, a CS+ odor main effect appeared; when ammonia was the CS+, subjects had more complaints across ammonia and niaouli than when the latter was the CS+ ($F(1,24) = 8.89$; $p < .005$).

To further differentiate the conditioning effect on complaints, it was tested for each of the complaint subsets. The data are summarized in Table 1. A highly reliable conditioning ($F(1,24) = 14.6$, $p < .001$) and conditioning × CS+ odor effect ($F(1,24) = 6.65$, $p < .02$) was observed for respiratory complaints. Also, unclassified complaints showed a significant Conditioning effect ($F(1,24) = 10.37$; $p < .005$). Simple main-effects tests showed significant effects when ammonia was CS+, but not when niaouli was the CS+. This was so for respiratory complaints ($F(1,24) = 20.48$, $p < .0001$), unclassified complaints ($F(1,24) = 10.69$; $p < .005$), and marginally for arousal complaints ($F(1,24) = 3.34$; $p = .07$). Tingling, cardiac, and dummy complaints were not affected.

Respiratory Behavior. Breathing frequency was conditioned ($F(1,24) = 5.26$, $p < .05$), but the conditioning effect tended to interact with CS+ odor ($F(1,24) = 3.19$, $p = 0.08$) (see Table 2). Simple main tests confirmed our finding with normal subjects (17) that the conditioning effect was only significant with ammonia as CS+ ($F(1,24) = 5.71$; $p < .05$) and not with niaouli ($F < 1$). Furthermore, a gender main effect was specified by a gender × conditioning interaction ($F(1,24) = 7.91$, $p < .01$): Female subjects showed a conditioned frequency effect ($F(1,24) = 9.87$; $p < .005$), but male subjects did not ($F < 1$). Figure 2 demonstrates that the CS+ odor × conditioning interaction was also significant for female subjects only ($F(1,24) = 6.15$; $p < .05$).

Tidal volume also showed a significant conditioning × gender interaction ($F(1,24) = 4.27$; $p < .05$): the pattern of results in male subjects (larger V_T's for CS+ than for CS− trials) was reversed in female subjects. A simple main effects test for male subjects when ammonia was CS+ showed a marginally significant conditioning effect ($F(1,24) = 3.41$; $p = .07$. It seems that female subjects responded most to the CS+ in the frequency domain, whereas male subjects responded in the volume domain (see Fig. 3).

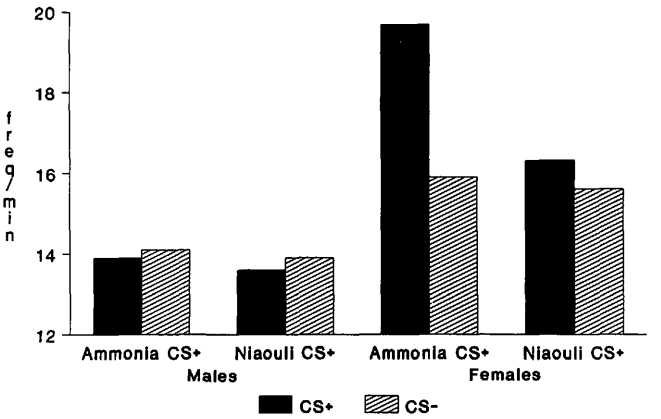

Fig. 2. The conditioning effect on respiratory frequency per minute as a function of gender and type of CS+ odor (ammonia or niaouli).

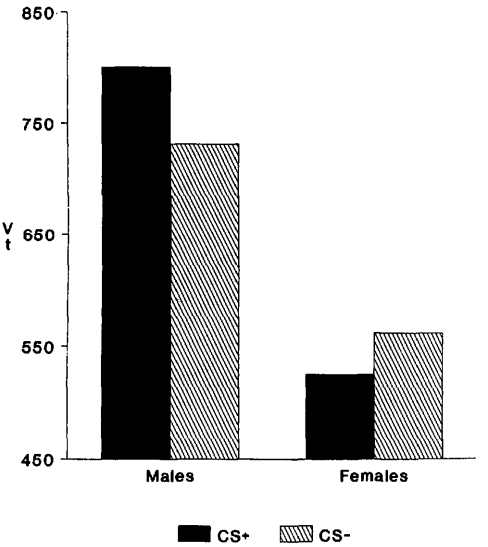

Fig. 3. The conditioning effect on tidal volume as a function of gender.

Minute ventilation showed a marginally significant effect of conditioning when ammonia was CS+ ($F(1,24) = 3.63$, $p = .06$) while $FETco_2$ was only affected by main effects of gender and trial. Heart rate was higher during CS+ than CS− (75 vs. 73 bpm), but only when ammonia was the CS+ ($F(1,24) = 6.65$; $p < .02$).

For both respiratory behavior and complaints, there were no differences between CS− trials of the test phase as a function of CS+ odor. Comparing CS− trials between acquisition and test showed that there were fewer complaints in the test phase ($F(1,24) = 5.7$; $p < .05$), but this difference did not interact with CS+ odor type ($F < 1$). The observed effects of ammonia during test were not caused by selective sensitization to this odor.

Comparison with Normal Subjects. Patient status participated in a significant status × gender × conditioning interaction for respiratory frequency ($F(1,48) = 5.11$; $p < .05$): the conditioning effect was stronger for female patients than for any other subgroup. Furthermore, patients overall had lower $FETco_2$ ($F(1,48) = 14.62$; $p < .0005$). For complaints, patient status appeared as a main effect (arousal, respiratory, tingling, and unclassified complaints). However, for respiratory and unclassified complaints, patients showed stronger conditioning effects than did normal subjects (respiration: $F(1,48) = 5.07$, $p < .05$; unclassified: $F(1,48) = 4.45$, $p < .05$).

Contingency Awareness and Odor Evaluations. When ammonia was the CS+, 13 out of 14 subjects indicated this odor as the one that had produced most complaints. When niaouli was the CS+, only nine subjects indicated this odor, two subjects indicated ammonia, and three subjects did not know. Although not significant (Mann-Wittney $U = 71.5$, $Z = -1.21$, $p = .22$; $Z_{adj} = -1.69$, $p = .09$), the data suggest some bias in the subjects' judgment of the

contingency between the type of odor and complaints during the acquisition phase, despite the absence of a CS+ odor by mixture interaction effect on self-reported complaints after each trial. After the test phase, this tendency was somewhat more pronounced ($U = 59$; $Z = -1.79$, $p = .07$; $Z_{adj} = -2.02$, $p < .05$), reflecting true differences in conditioned responding to the odors.

Ammonia was evaluated more negatively than niaouli after acquisition (−2.85 and + 0.67) and after test (−3.17 and + 0.32). Female subjects consistently scored the odors significantly more negatively than did male subjects, both after acquisition and test. Moment of measurement had no effect.

New Odors

Analyses were carried out using a gender × CS+ odor type (ammonia/niaouli) × type of new odor (rose/Ichtyol) ANOVA design.

Subjective Complaints. No differences in total complaint scores for the new odors emerged, nor was there any effect observable in the different subsets of complaints.

Respiratory Behavior. Male subjects had larger tidal volumes than female subjects ($F(1,24) = 9.33$; $p < .01$). This interacted with type of new odor for both f ($F(1,24) = 7.74$; $p < .02$) and V_E ($F(1,24) = 7.24$; $p < .02$): with the rose odor, female subjects breathed faster than male subjects, and male subjects had larger volumes than female subjects. These differences were not apparent with Ichtyol. No effects on respiratory behavior or complaints involved CS+ odor or CS+ odor × conditioning variables. This suggests that no generalization effects of conditioning were observed.

Correlational Analysis of Respiratory Behavior, Negative Affect, and Subjective Complaints in Psychosomatic Patients

Stepwise multiple regressions with forward inclusion of variables were run to explore the relationship between the complaints as caused by the conditioning procedure, the STAI-S, Blunting scale, and somatic reactivity. CS− trial values were subtracted from CS+ trial values for complaints on the one hand and respiratory and cardiac responses on the other hand. This was done for the total complaint score on the first and the second test trial, and for the different subset complaint scores after averaging across the two test trials. As can be seen in Table 3, increases in respiratory frequency, minute ventilation, and heart rate emerged as most pronounced predictors for increases in complaints. The STAI-S never appeared as a significant predictor, but the Blunting scale did: higher scores predicted fewer complaints.

DISCUSSION

The present data replicated the finding that a few experiences with a respiratory challenge in association with a specific CS+ are sufficient to alter respiratory behavior and induce psychosomatic

TABLE 3. Stepwise Multiple Regressions of Respiratory Frequency, Minute Ventilation, End-Tidal Fractional Concentration of CO_2 and Heart Rate (CS+ − CS− Trials) and Negative Affect on Total Complaint Scores per Trial and on Complaint Subsets, Averaged Across Two Trials; (CS+ Trials − CS− Trials)

	Criterion	Predictor	β	R	R^2-Change	p Value
Test	Trial 1	HR	0.46	0.58	0.34	.001
		f	0.41	0.70	0.15	.01
	Trial 2	V_E	0.56	0.56	0.32	.002
		Blunt	−0.47	0.73	0.22	.002
	Respiration	*f*	0.47	0.57	0.32	001
		HR	0.44	0.71	0.19	.005
	Arousal	HR	0.47	0.53	0.28	.004
		f	0.60	0.66	0.16	.01
		CO_2	0.40	0.75	0.12	.01
	Cardiac					
	Tingling					
	Unclassified	V_E	0.52	0.50	0.25	.008
		blunt	−0.33	0.60	0.11	.05
	Dummy					

[a] The order of predictors per criterion reflects the sequence of steps.

complaints upon experiencing this CS+ only (17). Respiratory frequency appeared as the more sensitive response parameter, especially in female subjects, whereas male subjects were inclined to respond more with tidal volume. Despite the subjects being psychosomatic patients with overall lower $FETCO_2$'s, conditioning did not affect respiratory behavior up to the level of causing additional hypocapnia. The conditioning effect on the total complaint score was mainly due to the effects on the respiratory and unclassified sets, and only marginally to conditioned general arousal. The effects could not be explained as the result of (selective) sensitization to ammonia and seemed highly specific: They did not generalize to odors that had not been present initially or to dummy complaints that were not experienced during CO_2 inhalation.

We also replicated the selective association effect: the conditioning effect was either more pronounced with or restricted to ammonia as CS. Several possible explanations can be advanced for this selectivity (see also 17): differences in preexisting associations, differences in associability based on affective similarity between CS and US (belongingness) (36), similarity between the ammonia CS and the CO_2 US at a physiologic level (irritancy), or differences in salience between the two odors. Future research is needed to sort out the different possibilities.

It is currently not clear which processes are responsible for the conditioned complaints. Correlational data suggested that conditioned somatic reactivity was, as in normal subjects, the best predictor of the reported complaints, whereas a hypervigilant, negativistic perceptual/attentional style as measured by the STAI (15) did not contribute to predicting the level of complaints caused by the conditioning procedure. The Blunting scale of the MBSS did contribute, however, in a negative way, whereas the Information Seeking scale did not correlate with subjective complaints. This suggests that the experienced complaints were somehow related to the somatic reactivity, but it is not clear whether accurate perception of bodily responses during the test mediated the effects, or whether these responses triggered memories/expectancies formed during the acquisition experience to shape the subjective experiences during the test phase (37).

The present study allowed for comparisons between psychosomatic patients and normal subjects from our previous study. However, these comparisons should be regarded as exploratory because the subjects were not matched for age and socioeconomic status. Also, normal subjects had two context exposure trials instead of one in both the acquisition and test phase, and acquisition and test were run on two consecutive days. In all other respects, the experiments were identical. In response to the questions that were advanced in the introduction, the data show that the patients' physiologic responses to the CO_2 challenge were not different from those of normal subjects,[2] nor did they report more arousal-related complaints (tension, anxious feelings, etc.). Nevertheless, patients had more complaints than normal subjects and this was so across CO_2 and air inhalation trials, although there were some weak tendencies for patients to have more respiratory (fast breathing, smothering sensations, etc.) and unclassified complaints (lump in throat, headache, dizziness, etc.) during CO_2 inhalation trials. For these same subsets of complaints, patients showed stronger conditioning effects than did normal subjects. In general, patients had more complaints during the test phase regardless of experimental conditions. Physiologically, patients showed, besides overall lower $FETCO_2$'s, stronger conditioning effects in respiratory frequency than did normal subjects, but this was confined to female subjects. The pattern of results suggests that patients are generally more attentionally directed to what happens in their body, but relatively more so regarding complaints of the respiratory and unclassified kind that typically occur in hyperventilation. This may facilitate conditioning of these complaints and, in female subjects, of respiratory frequency as well. The finding that female subjects are particularly vulnerable to conditioned respiratory frequency is of potential relevance to the well-known gender difference found for hyperventilation (18–20).

Assuming a functional equivalence at the subjective level between a hyperventilation episode and CO_2 inhalation, the present results may shed light on the finding that in some anxiety or somatoform disorders, psychosomatic complaints similar to those of hyperventilation can be registered (4) in the absence of hypocapnia (8, 4, 11). Because anxiety states in general are associated with a decreased PCO_2 level (38), occasional hyperventilation episodes are likely to occur during which situations or events may become CSs for conditioned physiologic re-

[2]Comparisons of an anxiety group (all subjects qualifying for anxiety disorder) with the combined mood and somatiform disorder groups did not reveal statistical differences, neither in complaints nor in respiratory behavior in acquisition and test. Within the anxiety group, seven patients suffered panic with or without agoraphobia; the others were generalized-anxiety patients and social phobics.

sponses and complaints. The selectivity of potential CSs for somatic complaints may become an interesting field of study, which may help to understand that some situations are more likely than others to trigger complaints (eg, hot, crowded, or closed places) or why women are more prone to developing agoraphobia than men (39). Because women are more inclined than men to rely on external cues to define their symptoms (40), external situations may have a higher probability to become CSs for complaints. Preliminary findings in our laboratory have further shown that mental images may act as CSs to alter respiration and induce complaints in a manner similar to that of the present odors (41), extending the relevance of this approach widely.

Because odors were used as CSs in the present study, the data may be relevant for conditions of multiple chemical sensitivity. Common symptoms include fatigue, difficulty concentrating, pounding heart, shortness of breath, anxiety, headache, and muscle tension (42). It occurs "in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms" (42). Panic-like reactions triggered by exposure to organic solvents have been observed (43). Explanations have referred to classical conditioning in which odors act as CSs and hyperventilation or acute overexposures to irritant gases are USs (44–46), but no experimental tests have been published. The present study documents the likelihood of such a hypothesis and may provide the "needed new paradigm" (47) to examine these phenomena in depth.

In summary, the present study shows that respiratory responses and associated psychosomatic complaints are subject to basic learning processes. The stability of results across two studies and two populations demonstrates that a well-defined conditioning paradigm may offer a look into the complex interaction between perceptual/attentional and other cognitive processes, on the one hand, and physiologic processes, on the other hand, that are involved in psychosomatic complaints.

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