

The somatic symptom paradox in DSM-IV anxiety disorders: suggestions for a clinical focus in psychophysiology

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Abstract

Although DSM-IV criteria for anxiety disorders include physiological symptoms, these symptoms are evaluated exclusively by verbal report. The current review explores the background for this paradox and tries to demonstrate on theoretical and empirical grounds how it could be resolved, providing new insights about the role of psychophysiological measures in the clinic. The three-systems approach to evaluating anxiety argues that somatic measures as well as verbal and behavioral ones are indispensable. However, the low concordance between these domains of measurement impugns their reliability and validity. We argue that concordance can be improved by examining the relationship of variables less global than anxiety and by restriction to specific anxiety disorders. For example, recent evidence from our and other laboratories indicate a prominent role of self-reported and physiologically measured breathing irregularities in panic disorder. Nonetheless, even within a diagnosis, anxiety patients vary radically in which somatic variables are deviant. Thus, in clinical practice, individual profiles of psychological and physiological anxiety responses may be essential to indicate distinct therapeutic approaches and ways of tracking improvement. Laboratory provocations specific to certain anxiety disorders and advances in ambulatory monitoring vastly expand the scope of self-report and physiological measurement and will likely contribute to a refined assessment of anxiety disorders. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994) and the similar ICD-10 by the World Health Organization set the worldwide accepted standards for the diagnosis of anxiety, mood, and other mental disorders. The criteria for diagnoses have been developed by consensus of leading psychiatrists and psychologists over several revisions of the manuals, integrating a variety of clinical observation and systematic research by epidemiologists, geneticists, therapists, psychophysicologists, and neurophysiologists. The classification of anxiety disorders that began with DSM-III (American Psychiatric Association, 1980) postulates a number of distinct diseases presumed to have distinct biological underpinnings. For example, family studies confirm that generalized anxiety disorder (GAD) and panic disorder (PD) are separate disorders (Noyes et al., 1987; Weissman, 1990), probably with different genetic backgrounds.

Although biological theories are advanced to explain differences among anxiety disorders, the overwhelming majority of evidence that led to the DSM-IV anxiety disorder categories derives from retrospective self-report data. At the current stage, DSM-IV and ICD-10 anxiety disorder diagnoses of individual patients are based solely on interviews where patients tell an interviewer what is troubling them, and the interviewer poses specific questions directed towards criteria of possibly relevant disorders. In research studies and clinical practice this information is gathered through structured clinical interviews such as the SCID (First et al., 1995).

Although DSM-IV has achieved a satisfactory interrater reliability for many diagnoses, the validity of any diagnostic category and patient diagnosis that solely rests on retrospective subjective reports, particularly subjective reports of somatic symptoms, is open to question. Table 1 lists the various somatic symptoms that are included in DSM-IV criteria for anxiety disorders. It is apparent that such symptoms play a critical role in the diagnosis of these disorders. However, while most other medical diagnoses (e.g. diabetes) rely on both symptom self-report and systematic biomedical measurements (e.g. the glucose tolerance test), no physiological measurements are required to confirm DSM-IV criterion symptoms. Table 1 lists a variety of physiological measures with face validity as measures of specific somatic symptoms. This list is not exhaustive and primarily includes measures that can be obtained noninvasively with currently available devices, even outside the laboratory, thus excluding techniques such as structural and functional MRI, PET scans, evoked brain potentials, echocardiography, and blood analysis. Some interoceptions, e.g. shortness of breath, are a product of perceptions related to chemical drive, the effort of breathing, and other factors that are currently not satisfactorily understood (Harver and Lorig, 2000). Some symptoms may involve processes such as venous vasoconstriction that are difficult to measure.

The current situation is paradoxical: both anxiety and its symptoms are evaluated exclusively by self-report, even when many anxiety symptoms have plausible physiological origins and most logically should be measured physiologically. In the following, we will explore the background for this paradox and try to demonstrate on theoretical and empirical grounds how it could be resolved.

Table 1

Possible associations between selected anxiety symptoms in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and physiological measures

Self-reported symptom	Physiological measure ^b
<i>DSM-IV Panic Attack^a</i>	
Palpitations, pounding heart, or accelerated heart rate	↑ stroke volume, pulse pressure, and/or heart rate, ↑ low frequency heart rate variability, ↑ ectopic beats
Sweating	↑ skin conductance
Trembling or shaking	↑ electromyographic activity
Sensations of shortness of breath or smothering	↑ minute ventilation and/or peak inspiratory flow, ↑ inspiratory pause, ↑ respiratory resistance
Feeling of choking	??
Chest pain or discomfort	Electrocardiogram abnormalities, e.g. ST-segment depression, ectopic beats? ↑ intercostal electromyographic activity?
Nausea or abdominal distress	↑ electrogastrographic activity
Feeling dizzy, unsteady, lightheaded, or faint	↑ vestibular abnormalities (e.g. in eye-tracking or vestibulo-oculo-reflex)
Paresthesias	↓ peripheral blood flow
Chills or hot flushes	↓ or ↑ body surface temperature or blood flow
<i>DSM-IV Posttraumatic or Acute Stress Disorder</i>	
Exaggerated startle response	↑ eye-blink startle response magnitude
Physiological hyperreactivity to trauma-relevant events	↑ changes in several response systems
Motoric restlessness	↑ electromyographic activity and/or limb movement
<i>DSM-IV Generalized Anxiety Disorder</i>	
Muscle tension	↑ electromyographic activity
Restlessness	↑ electromyographic activity and/or limb movement
<i>DSM-III-R Generalized Anxiety Disorder</i>	
Motor tension	↑ electromyographic activity and/or limb movement
Shortness of breath or smothering sensations	↑ minute ventilation and/or inspiratory flow rate
Palpitations or accelerated heart rate (tachycardia)	↑ stroke volume and/or heart rate, ↑ low frequency heart rate variability, ectopic beats
Sweating, or cold clammy hands	↑ skin conductance, ↑ or ↓ body surface temperature or blood flow
Dry mouth	↓ salivary flow rate
Dizziness or lightheadedness	↑ vestibulo-oculo abnormalities by electrooculography
Nausea, diarrhea, or other abdominal distress	↑ electrogastrographic activity
Flushes (hot flashes) or chills	↑ or ↓ body surface temperature or blood flow
Trouble swallowing or 'lump in throat'	↑ electromyographic activity
<i>DSM-IV Social Phobia</i>	
Embarrassment/blushing (not explicitly mentioned)	↑ facial surface blood flow
<i>DSM-IV Specific Phobia: Blood-Injection-Injury</i>	
Vasovagal fainting (not explicitly mentioned)	↑ respiratory sinus arrhythmia, ↓ blood pressure

^a May occur in Panic Disorder, Social Phobia, Specific Phobias, Anxiety Disorder Due to General Medical Condition, Substance-Induced Anxiety Disorder, Anxiety Disorder Not Otherwise Specified.

^b Only responses that can currently be measured relatively unobtrusively outside the laboratory were included in this list. As new devices become available, these measurement techniques will be refined and expanded.

2. The three-systems approach to emotion

The idea that physiological or other somatic variables are necessary for defining and quantifying anxiety was articulated in P.J. Lang's influential 1978 article (Lang, 1978). According to Lang's model, three systems of emotional response should be recorded: the verbal-cognitive (or language), somato-visceral (or physiological), and motor (or behavioral approach/avoidance) systems. His argument presented researchers and clinicians with a dilemma. On the one hand, no one of these response systems alone was adequate for assessing emotion as demonstrated by the low concordance between them. This was a strong rationale for including physiological measurements in assessing emotions in general and anxiety disorders in particular. On the other hand, the low concordance, which appeared to be rooted in the nature of emotion itself, seemed also to imply that emotional assessment could never be accurate. For example, Lang quoted studies in which correlations between putative physiological measures of anxiety (such as heart rate or skin conductance) and self-reported anxiety levels were on the order of 0.3–0.6, which means that they shared only 10–35% of the variance. Such correlations are unacceptably low to clinicians, since both clinical research and practice have always been based on what the client tells the clinician. Even Foa and Kozak (1998), who are generally sympathetic to the three-systems approach, writes about Lang's imagery paradigm using anxiety-provoking event scripts:

'The group differences found in the various studies suggest that patients with anxiety disorders show heightened reactivity when they imagine their feared material. Usually, an interview yields sufficient information for diagnosis and treatment planning, and physiological assessment is superfluous' (p. 682).

This emphasis on self-report as the gold standard for clinical assessment has only strengthened in the last decade because of two developments. One is the growing belief that cognitive distortions (i.e., beliefs about the dangerousness of certain situations and/or internal stimuli) are central to anxiety disorders (Clark, 1999). Cognitive therapies have proved to be quite effective in reducing anxiety, at least as assessed by self-report (Clark et al., 1994, 1999). Second, the biological paradigm promoted by pharmaceutical companies has stimulated much research in pharmacological treatment, the outcomes of which have always been evaluated solely by self-report.

2.1. *Inadequacy of individual response systems*

To decide whether the problem of low concordance is intractable, it is useful to consider how individual response systems fail to register fear and anxiety. The *behavioral system* can register avoidance, but not everyone with anxiety avoids the situations that provoke the anxiety. People can show courage in facing their fears, suppressing their tendencies to flee, or can give in to their fears and run away

(Rachman, 1990). A good example is panic disorder, where some individuals become agoraphobic and others do not. A goal of therapy is to have patients act courageous and stand their ground. Thus, gross behavior may or may not reflect fear.

Distrust of the *verbal-cognitive system* is high among psychoanalysts and the police, but unconscious defenses and lying are probably not the main reasons that self-reports of anxiety symptoms are an imperfect window into anxiety and its physiological concomitants. In addition to memory bias introduced by retrospective self-reports (Margraf et al., 1987), interoceptive acuity for symptoms associated with anxiety, such as palpitations, is low (Ehlers and Breuer, 1996), and self-report of symptoms is influenced to a high degree by situational, dispositional, and motivational factors (reviewed in Pennebaker, 2000). In certain people, or under certain circumstances, verbal reports of feeling anxious can be exaggerated or minimized because of lack of emotional awareness or vocabulary ('alexithymia') (e.g. Lane et al., 2000), semantic biases, selective attention, expectations, attitudes, or secondary gains. In addition, information processing is altered during intense anxiety (Eysenck and Calvo, 1992).

Another complicating problem is that identical responses on a Likert-type scale may represent different emotional intensities for different individuals because of differences in interpretations of the verbal anchors. For example, a panic disorder patient who has experienced degrees of anxiety unimaginable to a control subject may answer with a '40' on a 0–100 (not at all–extremely) SUD anxiety scale for anxiety levels that would be rated as 60 by controls.

Central to the understanding of *physiological responses* to emotion was the construct of activation or arousal, an integrated pattern of physiological change including reticular system activation, hormonal changes, and autonomic responses. Activation accompanies anxiety and other emotions, yet for several reasons, is flawed as a construct. Its validity is questionable since indicators of arousal such as skin conductance level, heart rate level, muscle tension, and EEG desynchronization correlate poorly (see for example, Fowles (1980), for heart rate and skin conductance). Organismic changes accompanying symptom report may occur independently in the electrodermal, skeletomotor, electrocortical, cardiovascular, ocular, gastrointestinal, and pulmonary systems. Each system has its homeostatic and protective function for the survival of an individual in the face of challenging situations. The patterning of the best adaptive response depends on the demand characteristics of the situation (situational response specificity) and biological and psychological characteristics of an individual (individual response specificity; Myrtek, 1984).

The concept of autonomic space challenges one common assumption of autonomic activation, namely, that sympathetic and parasympathetic nervous system activation are balanced against each other (i.e. activation in one means deactivation in the other branch; Berntson et al., 1991). It turns out that reciprocal activation is only one possibility. Furthermore, branches are not activated as a whole (Stemmler, 1993). We observed this in a recent experiment where heart rate decreased while blood pressure increased in socially anxious individuals while they were touched by

a stranger (Wilhelm et al., 2000b). In another of our experiments, stroke volume and heart rate were apparently adjusted independently to produce changes in cardiac output during psychological stress (Wilhelm and Grossman, 1997).

2.2. *Improving concordance*

Should the attempt to find physiological indicators of anxiety disorders and their somatic symptoms be forever abandoned on the basis of studies reporting low covariation with self-report? Will clinicians of the future solely rely on the self-reports of their anxious patients? We believe the answer is a definitive ‘no’. Bodily changes due to anxiety are not only a possible basis of specific patient complaints, they are an integral part of emotional expression, whether perceived (interoceived) by the subject or not. To emphasize one emotional response system to the exclusion of the others is overly simplistic and neglects an important aspect of the symptom presentation of patients. Here are some recommendations for improving concordance of clinically relevant measures of different response systems:

2.2.1. *Adopt an appropriate theoretical framework*

The framework of classical test-theory, which is commonly accepted in constructing questionnaires, rating scales, and structured interviews needs to be applied to physiological measures. One obstacle has been that three-systems theory rejects the basic assumption of test theory that anxiety is an underlying construct that can be measured by a set of somewhat correlated test items. We think that this rejection leads to a scientific deadend, and prefer the approach of Zinbarg (1998), who describes a hierarchical model in which anxiety is seen as a unitary, higher-order latent or hypothetical construct subsuming lower-level constructs, such as motivation, information processing, or arousal. Each of these can be measured in a variety of response systems by various empirical indicators. Because lower level constructs are conceptually more or less tightly linked (‘in proximity’) to the latent construct, and because interfering factors and measurement error specific to each measure distort this relationship during assessment, pairwise correlations between lower-level response system measures and higher-order constructs are necessarily less than perfect, and sometimes quite low. Nevertheless, these measures can be valid items or tests for the latent anxiety construct.

Furthermore, according to test theory, complete concordance is not the goal, since that would imply that items or tests were redundant. Rather concordance should be moderately high with different sources of error in the different tests. A composite measure of anxiety combining different measures as items on a test should be more powerful than any single item. For example, current DSM criteria for a panic attack are a composite set of self-report items with moderate intercorrelations. We propose adding physiological measures to this set, which would necessarily increase the validity of anxiety assessment within a multi-system test-theory framework. Of course, the benefits of increased validity of anxiety assessment will not become apparent unless clinicians assess information from systems other than patients’ self-report. Below (Section 3) we will give examples of

Table 2

Correlations between symptom self-report (0 = not at all to 3 = to a great extent) and physiological change measures in patients with flight phobia during flight ($N = 14$)

Physiological system	Self-report measure	Physiological measure	r
Dermal	'Sweating'	Skin conductance level	0.84
Pulmonary	'Shortness of breath'	Inspiratory flow rate	0.44
Cardiac	'Heart pounding or racing'	Heart rate	0.10

situations when physiological measures contain unexpected information that distinguishes anxious patients from controls.

2.2.2. *Look for correlates of less global constructs than anxiety*

While there may not be much covariation between lower-order latent variables like motivation and arousal, a correlation between a specific reported somatic symptom of arousal and a physiological measure of it could be quite high. That this is the case is illustrated by data from a recent study in our laboratory.

Twenty-eight women diagnosed with a specific phobia of flying undertook a short flight (12 min air time) with a commercial commuter-type airplane twice at a 1-week interval while physiological changes were monitored and symptom questionnaires were filled out at various points (Wilhelm and Roth, 1998a). Half of the patients received the tranquilizer alprazolam on the first flight and the other half placebo. Fifteen healthy controls completed only the first flight. In the following, we present analyses of the first-flight data of the 14 patients that had not received the tranquilizer. On average, these patients rated their anxiety while flying to be 7.4 on a 0 (not at all) to 10 (extremely) scale. Table 2 gives the correlations for flight minus baseline change scores between specific self-report and physiological measures. As can be seen, skin conductance level was an excellent measure of self-reported sweating, and inspiratory flow rate, a putative measure of shortness of breath (Milic-Emili, 1982), was moderately related to self-reports of shortness of breath.

2.2.3. *Find appropriate constructs and variable sets*

The low correlation of self-reported 'heart pounding or racing' with heart rate in Table 2 may be an example of choosing the wrong physiological variable. Even in panic attacks, the correlation between these two measures is only moderate (Margraf et al., 1987). One reason could be that many of these patients did not perceive tachycardia, but rather heart pounding, which would better be indexed by stroke volume. Recent evidence indicates that interoception of cardiac activation is more related to stroke volume than to heart rate changes (Schandry and Bestler, 1995).

Table 3 with data from the same study shows that change in heart rate correlated more poorly with change in self-reported anxiety than with change in self-reported desire to leave. It may be that desire to leave is the more relevant variable, since increased heart rate should be associated with the motivation to engage in motor

behavior to flee from a situation, a presumed latent variable. Of course, such behavior is not possible in an airplane, but the preparation for escape may occur nonetheless. In this data set, skin conductance level has a substantial correlation with self-reported anxiety, consistent with Fowles's assignment of skin conductance rather than heart rate to Gray's construct of the Behavioral Inhibition System (Fowles, 1980).

Other possibly relevant latent variables are excitement and novelty. Flying phobic patients on average endorsed an excitement level of 6.1 during flight (0–10 scale). For some patients who had avoided flying over many years, flying in an airplane was a novel experience, while this was not the case for others. Excitement and novelty may make their own distinct physiological contribution. Some theories (Barlow, 1988; Klein, 1980) distinguish between anxiety and panic, but the relative contributions of these were not evaluated in this study.

2.2.4. Control non-emotional sources of variance

Each measure has unique sources of error. Measurement error in physiological parameters can be minimized by averaging over longer recording epochs. With modern devices, physiological parameters can be measured easily and accurately outside the laboratory for long periods. In our study of flight phobia we chose to analyze a relatively short epoch of 2 min right before patients filled out symptom questionnaires in order to increase the temporal matching between measures. Medication use was controlled, but in general, psychotropic and other medications can distort how the autonomic nervous system relates to emotion. In this study we observed that alprazolam led to a dissociation of self-report and physiology during flying (Wilhelm and Roth, 1997a) by affecting only self-report.

Physiological systems have organismic functions other than expressing emotion, and these may preempt or distort emotionally induced physiological changes. For example, heart rate, minute ventilation, and many other cardiovascular and respiratory measures increase during physical activity to adjust for increased metabolic demands. Blood pressure and several other variables are affected by posture. Respiratory sinus arrhythmia is affected by respiratory rate and tidal volume

Table 3

Correlations of self-report and physiological change measures with self-reports of anxiety and desire to leave (0 = not at all to 10 = extremely) in patients with flight phobia during flight ($N = 14$)

	'Anxiety'	'Desire to leave'
<i>Self-report measure</i>		
'Sweating'	0.62	0.16
'Shortness of breath'	0.79	0.59
'Heart pounding or racing'	0.48	0.72
<i>Physiological measure</i>		
Skin conductance level	0.65	0.01
Inspiratory flow rate	0.15	0.06
Heart rate	0.37	0.22

(Hirsch and Bishop, 1981). Respiratory parameters are affected by speaking; skin conductance is affected by skin surface temperature and environmental temperature (Wilhelm and Roth, 1996). These distorting factors were held constant to a certain degree during the flying phobia study, but not perfectly.

Physical activity includes overt motor behavior and largely invisible isometric muscle contraction. In the flight phobia study we used several accelerometers to measure motility of trunk and limbs, which was not significantly increased during flight since subjects were sitting. Theoretically isometric activity can be measured by electromyography, though many electrodes would be required to monitor all the muscles. Under some circumstances, physically induced heart rate change can be partialled out from overall heart rate change using information from respiratory channels to provide a purified index of emotionally induced heart rate change ('additional heart rate'; Wilhelm and Roth, 1998b). A similar procedure can be applied to partial out skin temperature change from skin conductance change.

Elimination of simple measurement errors is the first essential step in analyzing psychophysiological data. Heart rate must be corrected for extrasystoles. Skin conductance measurement may need to be compensated for drifts over time and errors from electrode artifacts. Measurement of inspiratory flow rate (the ratio of tidal volume and inspiratory time) is computed from recordings of bands measuring changes in circumference of rib cage and abdomen. This measurement can be affected by trunk movement artifacts, inaccurate calibration, and drift over time, although precautions were taken in the flight phobia study to minimize these error sources.

Self-report data contain their own sources of error as discussed above. As much as possible, expectations and the demand characteristics of tasks need to be held constant across comparisons. In our flying phobia study, potentially interfering trait factors not controlled across groups included social desirability (which may have prompted some subjects to overreport symptoms), alexithymia (lack of emotional awareness), and active versus passive coping tendencies (active coping can be associated with a reduction in anxiety and an increase in physiological activation; Fowles, 1987). Several situational factors may have been important: Interoceptive acuity for heart sensations may have been particularly low because the noisy, shaky, and unstable environment of the airplane may have masked more subtle internal sensations related to heart activity. In contrast, the more obvious signs of sweating were readily perceptible. Patient expectations that accelerated heart rate is associated with elevated anxiety may have overridden any faint cardiac interoception, and reduced or spuriously increased covariation between self-report and physiology.

The intensely threatening quality of flying may have prompted some patients to dissociate. Recent evidence suggests that dissociators show attenuated physiological reactivity (Griffin et al., 1997). Particularly important in our study may have been selective attention and hyperawareness of specific external situational aspects (e.g. the view from the window, noises, shaking) at the cost of awareness of internal processes. Retrospective memory bias was likely not an important factor since subjects were asked to fill out the questionnaires during the flight and physiological measurements coincided with times of self-report.

2.3. *Future of the three systems approach*

In summary, we think that the three systems approach is applicable to anxiety disorders if, instead of trying to measure anxiety as a global construct, we use physiology as an additional way to measure somatic criterion symptoms, now assessed entirely by verbal report as outlined in Section 1. Yet, some practical barriers have to be overcome, especially in the case of panic disorder. Although we demonstrated good correlations between skin conductance level and self-reported sweating during exposure to one agoraphobic situation, the report of sweating during panic attacks must be validated by skin conductance levels during attacks, which usually occur outside the laboratory. This is a job for ambulatory monitoring but not an easy one, since panic attacks often occur less than daily, and continuous monitoring for days on end is not yet feasible. On the other hand, an interviewer can easily ask about past symptoms, although the reliability of retrospective reports diminishes the further back they go.

Since a prominent symptom reported by anxious patients is respiratory distress, we have focused in our recent research on the respiratory system, assuming that these self-reports are associated with specific physiological disturbances. In the following section, we will review background, empirical evidence, and applications pertinent to respiratory assessment in anxiety disorders, with a special emphasis on panic disorder. This will serve as an illustration of some of the points raised here. It will become clear that respiratory measurement can add valuable information to the assessment of anxiety disorders.

3. **The emerging role of respiratory disturbances in anxiety disorders**

A physiological system that has been widely neglected in the field of psychophysiology until recently is the respiratory system. This is surprising, since respiration is a physiological function situated strategically at the interface of mind and body. It is capable of operating automatically, its usual mode, but can be brought under voluntary control at least briefly. In contrast to autonomic functions such as heart rate or skin conduction, respiratory changes are perceivable if attention is focused on them. Respiration is essential for the maintenance of life, every organ system depending on proper gas exchange. Its regulation is subject to complex homeostatic mechanisms, and derangement of regulation can have severe health consequences.

Abnormalities in respiration have been postulated as central in anxiety disorders for several decades on the basis of patient reports of severe respiratory distress during anxiety episodes. Dyspnea (shortness of breath) is one of the most commonly reported symptoms of panic (Margraf et al., 1987; McNally et al., 1995), together with palpitations and faintness. Thus, one focus of the search for physiological markers for PD has been the respiratory system. In a further narrowing of this search, recent reports indicate that PD can be divided into subtypes with and without prominent respiratory symptoms (Aronson and Logue, 1988; Briggs et al., 1993; Shioiri et al., 1996). The respiratory subtype has been found to be more

physiologically reactive to CO₂ challenge (Biber and Alkin, 1999) and voluntary hyperventilation (Hegel and Ferguson, 1997). So far most research has not distinguished between these subtypes, which may have reduced effect sizes for respiratory markers and may explain some of the inconsistent findings. In the following, we review some of the evidence for respiratory abnormalities in anxiety disorders and present recent results from our laboratory. We will focus on PD because it is an exceedingly important anxiety disorder in terms of health care and societal costs and because of converging evidence that respiratory factors play a prominent role. Clinical observations suggest that panic attacks can also occur in social phobia and specific phobia, so it would not be too surprising if they show some of the respiratory features found in PD.

3.1. Hyperventilation

The ‘hyperventilation syndrome’ (Kerr et al., 1937) was believed to lie at the root of a variety of ‘psychosomatic’ complaints and mood disturbances, and since the establishment of PD as a diagnostic category, episodes of hyperventilation have been particularly associated with panic attacks (Ley, 1985). A symptomatic overlap in the two entities is apparent (Hornsveld and Garssen, 1997; Ley, 1985). In its basic form, this perspective postulates that hyperventilation (HV) itself produces the mood changes and symptoms (Lum, 1987) observed in anxiety disorders. This is a reasonable assumption since voluntary HV can lead to a pattern of physical and psychological symptoms in healthy individuals resembling acute anxiety symptoms, e.g. shortness of breath, palpitations, dizziness, faintness, or tingling in extremities.

Some empirical evidence supports the importance of HV. Voluntary HV has been used to provoke panic attacks in the laboratory (e.g. Gorman et al., 1984), and other panic provocations typically result in hypocapnia (low PCO₂) in anxious patients (e.g. Gorman et al., 1988b). Hypocapnia has repeatedly emerged as a difference between PD patients and comparison groups during baseline periods (Hegel and Ferguson, 1997; Papp et al., 1997). Rapee (1986) found that during a rest period before voluntary HV, PD patients had lower PetCO_{2s} (et = end-tidal) and higher heart rates than GAD patients. Munjack et al. (1993) reported that venous PCO₂ at rest (without the prospect of any stressor such as HV) was lower in PD patients than GAD patients, and that in GAD patients PCO₂ was lower than in controls. One of our recent analyses (Wilhelm et al., 2001b) confirmed that quietly sitting PD patients had lower PetCO₂ than either GAD patients or controls. In another study both PD and other anxious patients at rest had lower PetCO_{2s} than controls, and the anxious groups did not differ from each other (van den Hout et al., 1992). One study found evidence for chronic HV in panic patients before treatment and a normalization after treatment (Salkovskis et al., 1986). On the other hand, some studies have failed to find PetCO₂ differences between PD patient and controls (Holt and Andrews, 1998; Woods et al., 1986). *Slow recovery* of PetCO₂ after voluntary HV has also been found repeatedly in PD patients compared to healthy controls (Gorman et al., 1988a; Maddock and Carter, 1991). But

again, some studies did not find this slow recovery (Hegel and Ferguson, 1997; Rapee, 1986), which may have been due to the shorter HV (< 3 min) or recovery periods (< 5 min).

In spite of this evidence, other results have cast doubt on the importance of HV for PD and other anxiety disorders. First, voluntary HV is a relatively weak panic provocation compared to other biological challenges such as CO₂ inhalation and sodium lactate infusion (Gorman et al., 1988a, 1994; Papp et al., 1997). Second, when PCO₂ levels of PD patients are continuously assessed outside the laboratory using transcutaneous techniques (Garssen et al., 1994), only some spontaneous panic attacks are accompanied by hypocapnia (3/5: Hibbert and Pilsbury, 1988; 7/15: Hibbert and Pilsbury, 1989; 1/24: Garssen et al., 1996). Thus, ambulatory monitoring results seem to refute the idea that HV causes panic attacks or contributes to their symptoms or severity. However, this evidence cannot be viewed as conclusive for two reasons: First, ambulatory transcutaneous PCO₂ monitors have limitations in detecting arterial PCO₂ changes; e.g., their typical response time of about 2 min (due to slow diffusion of CO₂ through the skin) results in attenuation and temporal smoothing of PCO₂ changes so that small or short HV episodes may be missed. Second, the large variation in the fraction of panic attacks accompanied by hypocapnia across the studies cited above suggests that the composition of the PD samples differed in their proportions of respiratory subtype patients. This may also explain some of the contradictory results for baseline and HV recovery PetCO₂ levels cited above.

One of our recent studies examined the effects of exposure on respiration and a wide variety of other physiological parameters in patients with flight phobia (Wilhelm and Roth, 1998a). This agoraphobia shows a substantial overlap with panic disorder, and many of the patients in the study reported panic attacks during flight (Wilhelm and Roth, 1997b). Thus results may be generalizable to panic disorder. An analysis of the first-flight data of patients that had not received the tranquilizer and of controls showed that both groups showed a marked increase in respiratory rate and minute volume during flight, while only patients evinced respiratory anomalies such as extended pauses in breathing. In an ongoing study of driving phobia (another agoraphobia associated with panic disorder; Alpers and Wilhelm, 2000), we examined the effects of more prolonged and repeated unmedicated exposure sessions on respiration. The preliminary results indicate that exposure to feared driving situations causes immediate, marked changes in measures of respiratory physiology. While driving increases respiration rate equally in both groups, tidal volume is increased only in driving phobics, resulting in greater minute ventilation and lower PetCO₂ (35 mmHg at baseline to 28 mmHg during the first 30 min of exposure). Patient reports of less anxiety during the driving task after a few exposure sessions are reflected in synchronous changes in physiological measures towards levels of healthy controls. This study demonstrates that hyperventilation does play a role in anxiety and that ambulatory monitoring can help us understand what takes place during behavior therapy.

In another recent study we found that slow PetCO₂ recovery from HV in PD patients is not specific to the respiratory system, but is accompanied by a lag in

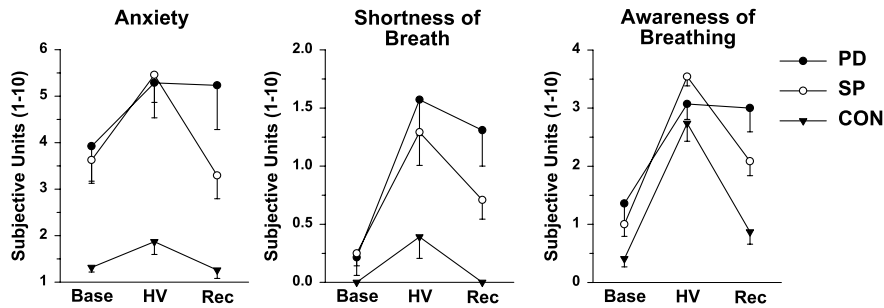


Fig. 1. Means and standard errors for self-reported anxiety, shortness of breath, and awareness of breathing during the experiment for patients with panic disorder (PD), social phobia (SP), and for normal controls (CON). Base, baseline; HV, hyperventilation; Rec, recovery.

normalization of a variety of autonomic and experiential measures (Wilhelm et al., in press-a). We recorded respiratory, autonomic, and experiential responses in 14 patients with PD, 24 patients with social phobia (SP), and 24 controls during six cycles of 1 min of fast breathing alternating with 1 min of recovery, followed by 3 min of fast breathing and 10 min of recovery (see Figs. 1 and 2). Speed of fast breathing was paced by a tone modulated at 18 cycles/min, and depth by feedback aimed at achieving a P_{etCO_2} of 20 mmHg. During fast breathing all three groups reached equal respiratory rates, minute volumes, and P_{etCO_2} s. However, PD and SP patients reported more anxiety than controls, and their feelings of shortness of breath and suffocation increased more from baseline. Skin conductance, a measure of sympathetic activation, declined more slowly in PD over the six 1-min fast breathing periods (Fig. 2b). At the end of the 10-min recovery, PD patients reported more awareness of breathing, shortness of breath, and fear of being short of breath (not shown), and their P_{etCO_2} s, heart rates, and skin conductance levels had returned less towards normal levels than in other groups (Fig. 2a–c). These results indicate that PD and SP patients report more distress than controls to equal amounts of hypocapnia, but PD differ from SP patients and controls in having slower symptomatic and physiological recovery.

3.2. Respiratory variability

That anxious subjects sigh more frequently than comparison subjects has been reported since accurate measurements of continuous breathing were first made. Devices that produced spiograms permitted quantification of tidal volumes, and ‘psychoneurotic’ patients were observed to sigh frequently (Finesinger, 1943). The frequency of sighs measured with inductive plethysmography distinguished chronically anxious patients from patients with asthma, chronic obstructive pulmonary disease, restrictive lung disease, and primary pulmonary hypertension (Tobin et al., 1983). Anxious individuals who sigh frequently have been observed to have normal total lung capacity, but lower vital capacity and higher residual capacity (Aljadeff et al., 1993). Lactate infusions, which increase anxiety especially in PD patients,

increased sighing in PD patients (Schwartz et al., 1996). Sigh breaths are often quantified as breaths with a tidal volume exceeding twice the tidal volume of surrounding breaths. Sighs can be a reason for within-subject variability of tidal volumes, which can be quantified by statistics such as standard deviation, coefficient of variation, or the mean square successive difference (von Neumann statistic).

Abelson et al. (1996) evaluated the panicogenic effect of the respiratory stimulant doxapram in 16 PD patients and 16 matched controls. A cognitive intervention that

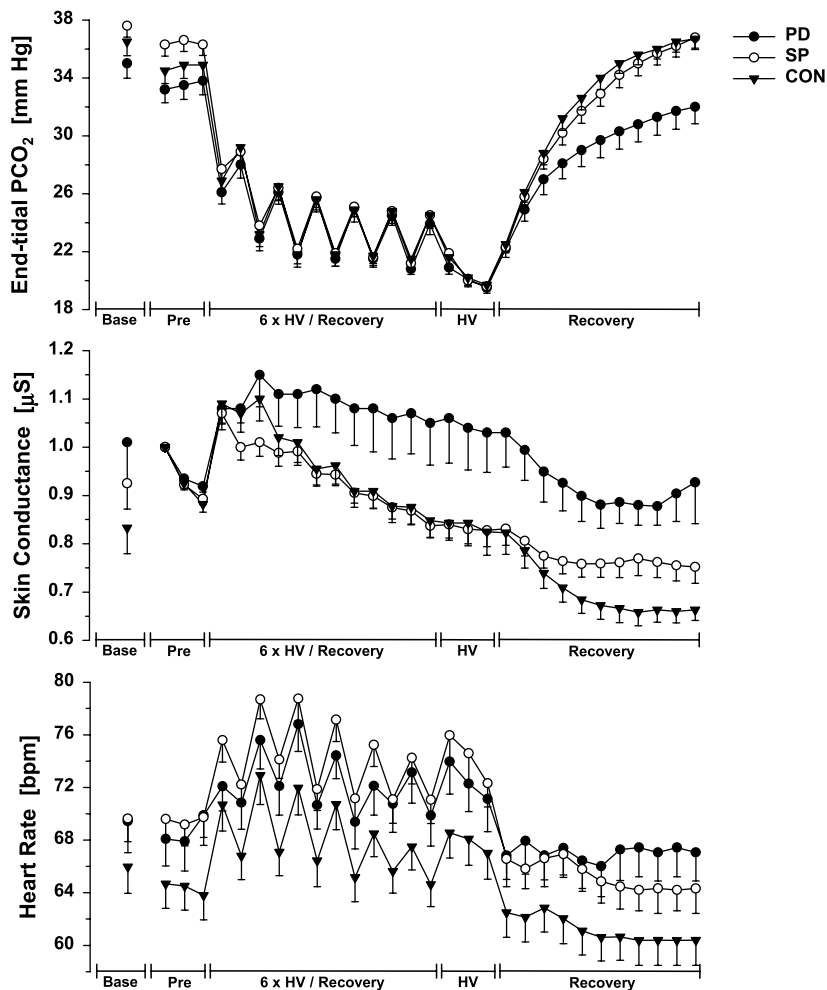


Fig. 2. (a)–(c) 1-min means and standard errors for the physiological measures PCO₂, skin conductance (for illustration of time effects expressed as relative change in relationship to the beginning of the anticipation phase), and heart rate during the experiment for patients with panic disorder (PD), social phobia (SP), and normal controls (CON). Base, baseline; pre, anticipation; HV = hyperventilation; Rec = recovery.

was designed to reduce panic response by reassuring half of the subjects in each group of the benign nature of symptoms substantially attenuated the excessive hyperventilatory response of patients. A reanalysis of the data (Abelson et al., 2001) showed that patients had large elevations in tidal volume variability compared to controls in all phases of the experiment—baseline, doxapram challenge, and recovery. Neither the cognitive intervention nor doxapram-induced hyperventilation produced significant changes in this respiratory irregularity. Patients also had elevations in respiratory rate variability, though not as prominently or persistently.

Stein et al. (1995) examined the nocturnal breathing patterns of 14 PD patients and 14 matched controls to determine whether PD patients had respiratory irregularities at a time when anxiety was not manifest. During REM sleep, patients had increased tidal volume variability and a higher frequency of 5–10 s breathing pauses. Bystritsky et al. (2000) compared physiological responses of 42 PD patients with 25 matched controls during baseline, 5% CO₂ inhalation, and recovery. A subgroup of 12 patients experienced panic attacks during the CO₂ inhalation and they showed increased respiratory variability (quantified as length and number of breathing pauses and respiratory rate variability). Consistent with results from studies of adults with PD, tidal volume variability also differentiated children and adolescents with anxiety disorders from psychiatrically healthy children during a baseline before CO₂ inhalation (Pine et al., 1998).

Some of our recent analyses used complex demodulation to quantify tidal volume variability. This method is more precise than the conventional measures for describing oscillatory variability within distinct frequency bands. We found higher tidal volume variability within the spectral band of 0.004–0.14 Hz, corresponding to period lengths of 6.6–240 s in PD patients compared to GAD patients or controls during baseline (Wilhelm et al., 2001b). This variability was not entirely due to sighs as we defined them, since after deletion of sigh breaths and their replacement with interpolated values, PD patients still had higher tidal volume variability than controls. A motivation for this study was to look for unprovoked fluctuations in biological features known to be associated with full-blown attacks. Cardiovascular, respiratory, and electrodermal variables sensitive to anxiety seemed like good candidates but, surprisingly, only respiratory variables showed group differences. Fluctuations in cardiac output and other hemodynamic variables, which one might expect with intermittent sympathetic discharge, did not distinguish the groups.

We also observed increased tidal volume variability (quantified by complex demodulation or sigh frequency) in PD patients during recovery from hyperventilation in the study described above (Wilhelm et al., in press-a). Since low PetCO₂ in PD patients was not accompanied by increased minute volume, the mechanism for impeded recovery from hypocapnia induced by voluntary HV appeared to be higher rates of sighing.

To further examine the role of sigh breaths for respiratory regulation in PD patients, we conducted a detailed analysis of the respiratory variability study described above (Wilhelm et al., 2001a). Surprisingly, sigh frequency was more predictive of individual PetCO₂ levels than was minute volume. Ensemble averaging

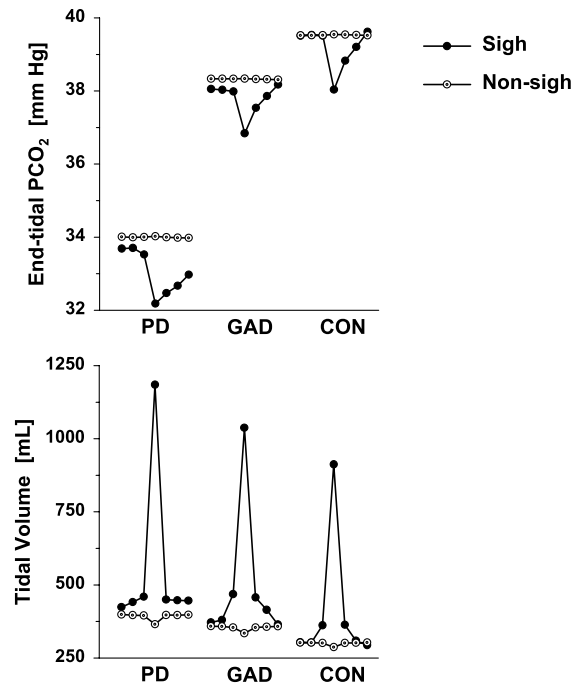


Fig. 3. Sigh and nonsigh ensemble averages of PCO₂ and tidal volume for patients with panic disorder (PD), generalized anxiety disorder (GAD), and normal controls (CON). Averages are of the three breaths preceding a sigh, the sigh, and the three breaths following the sigh. Reproduced with permission.

of respiratory variables for sequences of breaths surrounding sighs showed that before sighs PetCO₂ was reduced and tidal volume increased in all groups (Fig. 3). Sigh breaths were larger in PD patients than controls. After a sigh, PetCO₂ and tidal volume did not return to baseline levels as quickly in PD patients as in controls. These data suggest that hypocapnia in the PD patients was related to their increased frequency of sighing.

3.3. *The state-trait distinction*

Although it is apparent from the previous paragraphs that respiratory disturbances play an important role in mediating anxiety symptoms, it is not so clear to what extent they represent a 'state' anxiety effect or a persisting 'trait' characteristic of anxiety patients. Akin to the idea of trait is that of 'marker', which is a somatic abnormality restricted to a single, defined clinical group. In contrast to mediators, markers are not necessarily causally related to the disorder they mark. Markers could be particularly useful in genetic studies by providing an 'endophenotype' (Klein, 1998) of a specific disorder. The establishment of markers for anxiety disorders could also lead to more accurate assignment of patients to DSM-IV categories or to new diagnostic classifications.

In certain studies, respiratory abnormalities appeared only during anxiety provocations, which could be a sign of a state effect. If the provocation produced abnormalities in only one diagnostic group, a state-trait interaction might be present. Only few of the cited studies (Hegel and Ferguson, 1997; Holt and Andrews, 1998; Munjack et al., 1993; Rapee et al., 1992; van den Hout et al., 1992; Wilhelm et al., in press-a, Wilhelm et al., 2001a,b) evaluated if respiratory abnormalities were specific to one of two or more equally anxious patient groups (e.g. PD vs. GAD or Social Phobia). Results of these studies generally (except: van den Hout et al., 1992) support the contention that respiratory dysregulation is a biological marker for PD, although other anxiety disorders may show similar abnormalities to a smaller degree.

Provocations in our laboratory have included CO₂ inhalation (Roth et al., 1992), repeated breath holding (Roth et al., 1998b), prolonged quiet sitting (Wilhelm et al., 2001a,b), mental stress (Grossman et al., 1996, 1997), hyperventilation (Wilhelm et al., in press-a), giving a speech in front of others (Gerlach et al., 2001; Hofmann et al., 1995), and approaching a phobic stimulus (Roth et al., 1994). We also have demonstrated the feasibility and utility of measurements in anxiety-producing situations outside the laboratory: flying in an airplane (Wilhelm and Roth, 1998a), driving a car on the freeway or over bridges (Alpers and Wilhelm, 2000), walking through a shopping mall (Whittal et al., 1996), and everyday activities (Margraf et al., 1987).

Our recent studies utilized a number of methodological improvements: special transformation techniques to enhance the statistical power of physiological measures to detect differences between specific anxious and non-anxious groups, transfer function assessment of respiratory sinus arrhythmia (Wilhelm et al., 1998, 1999), complex demodulation to assess instability in physiological measures (Wilhelm et al., 1997, 2001b), skin conductance slope transformations to assess recovery (Roth et al., 1998a), 'additional heart rate' measurement to partial out physically induced heart rate increases (Wilhelm and Roth, 1998b), and ensemble averaging to elucidate interrelationships between breaths (Wilhelm et al., 2001a). In addition, we developed procedures to control for interfering factors in ambulatory monitoring (Wilhelm and Roth, 1996).

An advantage of ambulatory measurement outside the laboratory is being able to determine to what extent a physiological characteristic is a trait feature persisting over 24 h, or a shorter-term state induced by the laboratory itself. Supposed laboratory baselines hardly represent a prototypic, basal state, since they are influenced by at least three acute factors: what went on before them (clinical tests, respiratory challenge procedures), the experimental conditions of baseline (such as the invasiveness of the breathing measurement apparatus, the confining quality of the testing room), and what the subject anticipates will happen after them. Patients with anxiety disorders are often particularly anxious in the laboratory.

Ambulatory recording is rare for the measurement of respiratory variables in anxiety. A notable exception is a 24-h ambulatory study from the Columbia group (Martinez et al., 1996) using a portable respiratory monitor. Tidal volume averaged for 2-min periods showed larger variability in PD patients than in matched

controls. Tidal volume, rather than respiratory rate increases characterized the periods of anxiety and limited symptom attacks. These results indicate that PD patients experience large fluctuations in anxiety during everyday life that are accompanied by changes in tidal volume over periods of minutes, in addition to the breath-by-breath dysregulation observed in the laboratory. Unfortunately, the monitor did not allow recording and full-disclosure analysis of respiration. Breath-by-breath variability in breathing is concealed by on-line averaging of measurements. In addition, unsupervised automatic analysis may have compromised the results. Respiratory patterns are complex and can be distorted by a variety of artifacts (Wilhelm and Roth, 1998c). In a recent chapter (Wilhelm et al., in press-b) we describe our new methodology of full-disclosure ambulatory assessment of breath-by-breath respiratory pattern variability and end-tidal PCO_2 that will help expand our current knowledge base on respiratory factors in anxiety disorders.

3.4. Efficacy of respiration focused therapy

Based on the above results, respiratory feedback and training would seem to be a logical treatment for PD. Breathing training is a part of many behaviorally or cognitively oriented treatment packages, of most meditative arts, and of other somatic therapies. In a recent review of mechanisms underlying fear reduction in psychotherapy, Marks and Dar (2000) call for more research to identify therapy components that reduce each facet of fear (cognitive, behavioral, and physiological). Specifically, they suggest that the respiratory components that are often part of comprehensive cognitive-behavioral treatment programs, deserve study in their own right. Unfortunately, despite widespread clinical usage, only limited systematic data exist on the efficacy of breathing training or PetCO_2 feedback (Bass, 1994). When breathing therapies have been shown to be effective, critics have claimed that any success was the result of cognitive rather than physiological change (de Ruiter et al., 1989; Salkovskis et al., 1986). In fact, it is probably impossible to teach breathing to symptomatic people without changing their cognitive interpretations of their symptoms (Ley, 1991).

Preliminary evidence for the efficacy of breathing training for treating anxiety disorders comes from Grossman et al. (1985), who assigned 47 patients with symptoms of anxiety and hyperventilation syndrome (an older diagnosis overlapping substantially with PD) to one of two groups: breathing training focusing on slow paced breathing and using ambulatory respiratory rate feedback, or a comparison group receiving placebo treatment. The training group showed more reduction in symptoms than the comparison group. Furthermore, symptom reduction was related to changes in respiratory parameters. Creager and Gevirtz (2000) recently compared a standard cognitive protocol for PD treatment with a capnometer feedback assisted breathing training. Both groups showed dramatic improvement, not differing from each other. Another study in our laboratory (Wilhelm et al., 2000a) is examining in detail the ambulatory and laboratory respiratory characteristics (such as baseline PetCO_2 , speed of PetCO_2 , recovery from voluntary hyperventilation, tidal volume variability) of PD patients during the course of an

intensive capnometer feedback assisted breathing training performed at home. This study was stimulated by the practice of clinicians who claim that capnographic feedback is invaluable therapeutically (Timmons and Ley, 1994).

4. Individual centered psychophysiology: profiling as clinical tool

It was recognized early that physiological activation patterns are affected by individual differences apparently unrelated to anxiety or stress, which was termed *individual response specificity* (Lacey, 1967; Myrtek, 1984). However, such individual differences in anxious patients may relate to different symptom patterns of the kind recognized in the DSM-IV panic criteria, which require only four out of a list of 13 possible symptoms to be present to qualify for panic. The pattern of symptoms endorsed by anxious patients shows some commonalities — palpitations, dizziness, and shortness of breath are relatively common — but, there are great interindividual differences in symptoms reported (Margraf et al., 1987) that may correspond to specific physiological response patterns.

Although on average phobic participants in the flight phobia study did not respond with significantly greater ventilation to the flight than controls, an inspection of individual response patterns indicates that some patients showed extreme levels of hyperventilation, like patient 9 shown in Fig. 4. Other patients showed very high heart rate levels during the flight, like patient 26 shown in Fig. 4.

In order to visualize and compare activation patterns of different subjects, change scores (flight minus baseline) for several putative self-report and physiological measures were standardized (mean = 50, SD = 10) using controls as a reference population ($t\text{-score} = \{\text{change score} - \text{average change score of controls}\} / \text{SD of change score of controls}$). To achieve a consistent direction of activation across variables, the polarity of RSA and finger temperature was reversed. Fig. 5 depicts three typical profiles of phobic patients, which demonstrate the large differences in activation patterns. All three patients meet current DSM diagnostic criteria for specific phobia (flying). However, every clinician would probably agree that these patients differ in the self-reported and physiological manifestations of the disorder. Patients 1 and 14 were more than one standard deviation (10 units) above the control reference (50) in most measures, while patient 13 was elevated ($t\text{-score} > 60$) only in self-reported anxiety, finger temperature decrement, and minute ventilation. Patients 1 and 14 had abnormally long inspiratory pauses and both complained of shortness of breath. With respect to autonomic measures, patient 14 showed highest reactivity in additional heart rate and RSA decrement, while patient 1 showed highest reactivity in skin conductance.

These profiles are based on responses to a single situation, flying in an airplane. Another kind of variation in activation is situational response specificity. For example, exposure to blood or injury tends initially to cause decreases in heart rate and blood pressure, whereas making a speech causes increases in both. Individuals who have specific kinds of fears will have a distinct profile of response in various fearful situations, an interaction between the individual and the situation that can

be termed individual-situational response specificity. People with one fear are more likely to have multiple fears. Had we tested the phobic participants in the flight phobia study in multiple potentially anxiety-provoking situations, they probably would have reacted strongly to several.

4.1. Multi-channel testing: activation profiles

In order to obtain comprehensive profiles, multiple channels should be measured. In the domain of physiology, these include respiratory, cardiovascular, electrodermal, and hormonal assessments. A somewhat different measure is eye-blink startle, which has been studied intensively as a probe of the viewing of affectively laden pictures (Lang et al., 1990). Startle potentiation has been linked to circuits in the amygdala, a basic emotion processing center in the brain. The eye-blink startle reflex response has been shown to discriminate different anxiety disorders (Hamm

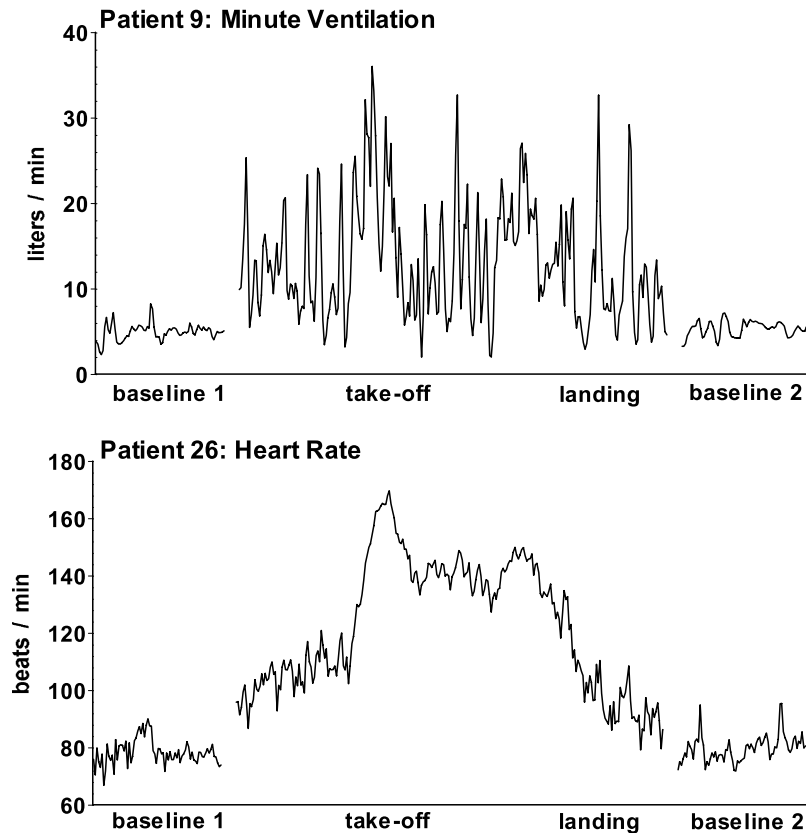


Fig. 4. Minute ventilation of patient 9 during a 5-min pre-flight baseline, in the airplane right before and during take-off and landing (17 min), and during the post-flight baseline. The heart rate of patient 26 is plotted during equivalent intervals. Data are 10-s moving averages.

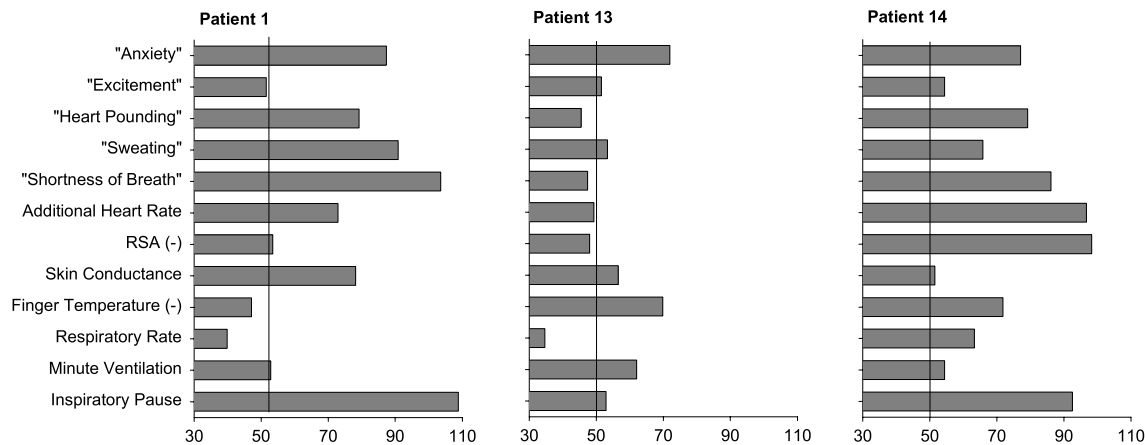


Fig. 5. Standardized activation profiles for individual patients in the flight phobia study. Self-report items are in parentheses. The polarity of RSA and finger temperature is reversed. *t*-scores for flight-baseline change scores based on reference control population (mean = 50, SD = 10). See text for further explanation.

et al., 1997). Excessive startle is a symptom that, when reported verbally, is one of the criteria for the diagnosis of PTSD (see Table 1).

Activation profiles are analogous to the list of criterion symptoms for panic attacks. Some of the profile items, like skin conductance, correlate directly with symptoms on this list, in this case, sweating (see also Table 1). This suggests that activation profiles could be added to, or integrated with, diagnostic criteria for specific anxiety disorders in order to give a more accurate and reliable diagnosis. In addition, they could be part of a composite measure of the severity of illness, of utility in measuring treatment outcome. For this to happen, however, research would have to demonstrate at least a moderate relationship of physiological profile items with conventional (verbal) clinical diagnoses and severity of illness. Another step in establishing the importance of such profiles would be to show that under certain circumstances these profiles would not correspond to verbal report, indicating more or less treatment response than did verbal report. For example, attitude-changing therapies might normalize measures in the verbal report domain more than measures in the somatic domain.

The practicality of profiles for diagnosis depends on a number of factors. Items on the profile that represent traits or vulnerability to an anxiety disorder will be present regardless of when or under what circumstances the recording is done. DSM-IV diagnoses are given to persistent or recurring symptoms, which are not necessarily permanent states, so trait measures that purely represent proneness to an anxiety disorder will not be appropriate for diagnosis. Items on the profile that represent temporary states are also insufficient, since diagnosis depends on the history of the illness, its mode of onset and course as well as its current manifestations. Physiological recording cannot provide historical information, but only an assessment of what is going on now or how an individual reacts to currently experienced natural or contrived situations. Careful selection of diagnosis specific testing situations can much improve the validity of physiological assessment.

4.2. Multi-situational testing: test batteries and ambulatory monitoring

Anxiety can be quite situationally bound, e.g. in specific or social phobia, or can be primarily non-situational and sustained, e.g. in generalized anxiety disorder (GAD). Some disorders may be best characterized by a mix of those two types. For example, panic disorder (PD) patients react specifically with fear to CO₂ inhalation provocations, but also may show elevated anxiety levels throughout the day because of fear of impending panic attacks. This sustained anxiety might be captured by elevated levels across different situational tests in the clinic, but probably can best be assessed by monitoring physiological responses of patients ambulatorily during an entire day and night.

A clinical assessment battery would include a variety of situations that are specific stressors for different anxiety disorders, e.g. enclosed spaces, heights, darkness, the sight of blood, theatres, or driving. Twenty-four hour monitoring may also be helpful in capturing sudden surges in activation associated with PD (Roth et al., 1998a), or longer-term respiratory instability (Martinez et al., 1996).

GAD patients would best be assessed during an entire day to determine if they have a generally elevated activation profile. In the case of flight phobia, virtual reality simulation may be an adequate way to elicit the response. Slides, videotapes, and mental imagery have been used to study specific phobia and PTSD. Although the physiological responses are comparatively small, they can be reliable under tightly controlled conditions. Self-reports of the intensity of experienced symptoms and anxiety can be systematically captured in the laboratory and outside of it by a keypad that is connected to the monitoring system (Jain et al., 1996). Intervals when patients reported high levels of anxiety or specific symptoms would receive special attention in the analysis of the data.

An additional complexity to the interpretation of profiles from different situations is that physiological reactions to anxiety-producing stimuli can vary with the nature of the stimulus. For example, blood or injury stimuli often produce a vasovagal reaction and painful stimuli, a beta-adrenergic reaction (situational response specificity, Myrtek, 1984). In some situations, profiles may be influenced by factors other than emotion. Physical activity, speech, and posture have profound effects on autonomic variables, and these effects must be taken into account if emotional activation is to be discerned. Speech effects complicate the interpretation of speaking tests for Social Phobia. Physical activity is often an interfering variable in agoraphobic situations. Our method of ambulatory assessment of additional heart rate enables us to measure emotional heart rate increase even when patients are physically active (Wilhelm and Roth, 1998b).

The ambulatory setting has some advantages over the laboratory for assessing the biology of anxiety (Turpin, 1990). Although the laboratory provides control of stimulation and motor activity, it is not typical of a person's ordinary life. The laboratory environment is a novel and fear-inducing one for many subjects, so the results of measurements in it may be poorly generalizable to more natural settings (Fahrenberg et al., 1986). The laboratory window of observation is limited in time to a maximum of a few hours. Infrequent events like spontaneous panic attacks are easy to miss. Using ambulatory monitoring, physiological reactions related to anxiety can be recorded when and where they happen, including within the laboratory. Ambulatory monitoring, however, presents its own special difficulties. Our recent study of flying phobics has suggested new ways to deal with some of them (Wilhelm and Roth, 1996). Control of transducer artifacts in active subjects is a particular problem for some response channels. The data set recorded is often gigantic, requiring complex and fast computer programs for data analysis and reduction.

4.3. Treatment matching

An example of how ambulatory physiological data can provide information useful for treatment of an individual is the case description by Hofmann and Barlow (1996). Using 24-h heart and respiratory rate monitoring, the therapist was able to establish that the panic attacks of the patient did not come 'out of the blue', as the patient assumed, but rather were preceded by increased ventilation. In

addition, since the monitor showed that her heart rate increased only after panic attacks, and not before, this could mitigate her fear that the attacks were caused by a heart condition. A comparison of the patient's self-report data before and after wearing the device indicated that this therapeutic strategy had a beneficial treatment effect. Here, physiological data were used as information to change a patient's attitudes about her panic attacks. In our clinical experience, patients are highly interested in what kind of somatic response profile they have when they are anxious. Measuring the quality and intensity of reported somatic symptoms objectively can be a reassuring experience for patients. Patients recognize that after all 'it's not all in their minds'. This can increase the rapport between patient and therapist and patient compliance with the treatment regimen.

Another potential use of psychophysiological profiling is to tailor the treatment to the individual patient. Based on the profiling data, treatment assignment for panic disorder patients could be as outlined in Table 4. For example, if heart rate change in response to an anxiety provocation is abnormally high (e.g. one standard deviation above the control population, i.e. a *t*-score of 60), exposure exercises could focus on physical exercise like stair-climbing. If minute ventilation is abnormally high, treatment could focus more on exposure to hyperventilation and on breathing training. If reports of heart pounding or racing are high without being substantiated by heart rate or stroke volume increase, or if reported shortness of breath is high without changes in respiratory measures, treatment could focus more on cognitive restructuring.

If a subtype of DSM-IV anxiety disorders can be characterized by a specific physiological profile, targeting this abnormality directly with a specific treatment would yield better results than a more unfocused cognitive-behavioral treatment program or medication. For example, treating a respiratory subtype of anxiety disorders (Aronson and Logue, 1988; Briggs et al., 1993; Shioiri et al., 1996) with a respiratory therapy would be sensible. DSM-IV self-report based boundaries between disorders may not map well into physiological differences: this respiratory subtype could exist not only in PD but also in GAD and in specific or social phobia.

A few studies have examined whether matching the therapy to the most abnormal anxiety domain (cognitive, behavioral, or physiological) improves treatment outcome. An earlier study (Öst et al., 1982) found that higher heart rate in claustrophobics in a small test chamber predicted better response to Applied Relaxation than to exposure or cognitive treatment. Later studies, however, did not find differential treatment effects when treatments for Agoraphobia (Öst et al., 1984), Social Phobia (Jerremalm et al., 1986a), dental phobia (Jerremalm et al., 1986b) and acrophobia (Menzies Ross and Clarke, 1995) were evaluated. One problem with these studies that limits the conclusions that can be drawn from them is that their indices of physiological activation were either heart rate or skin conductance rather than broadband activation profiles. As discussed above, because of individual response specificity, relying on a few physiological measures may be insufficient.

Table 4
Possible treatment matching for patients with panic disorder

Primary physiological response system	Physiological marker	Interoceptive marker	Treatment focus
Cardiac	Heart rate, stroke volume, pulse pressure	Heart racing or pounding	Exposure to physical activity
Electrodermal	Skin conductance level	Sweating	Relaxation training, physical activity
Pulmonary	Minute ventilation, inspiratory flow rate, end-tidal PCO ₂ , tidal volume or respiratory rate irregularity	Shortness of breath	Breathing training, PCO ₂ biofeedback, slow and regular paced breathing
Peripheral vascular	Skin surface temperature	Cold hands, tingling or numbness in extremities	Relaxation or autogenic training
None	N/A	Any of the above	Cognitive restructuring

Although cognitive-behavioral and psychopharmacological treatments have shown high success rates in several anxiety disorders (as assessed by interview and questionnaires, on the order of 60–80% of patients are symptom free at the end of treatment and follow-up) recent data indicates that relapse in PD is common (Barlow et al., 2000). The factors contributing to relapse are not well understood. One could be that physiological disturbance specific to the treated individual was not addressed. Targeting the persistent respiratory abnormalities in many PD patients with specific behavioral or pharmacological treatment modules, might improve the degree and permanence of treatment success.

4.4. Profiling: outlook

With the rapid advances in microelectronics, devices measuring a wide variety of bodily functions and motoric behaviors in addition to self-report data over periods of hours or days will soon be inexpensive, easy to use, and unobtrusive. ‘Wearable computers’ with electrophysiological sensors integrated in clothing to provide real-time feedback about physiological activation are currently being developed (Picard, 1997). Existing physiological monitors are so rugged, portable, and automatic that they record accurately from moving subjects in various settings of daily life (e.g. the Vitaport 2 system used in our laboratory, see Jain et al., 1996). An important recent development that will make it easier to set up the array of sensors necessary for multi-channel recording is the LifeShirt™ (Vivometrics, Inc., Ventura, CA). This device is worn like a shirt and includes sensors and cables for measurement of respiration, electrocardiogram, inductive cardiogram, and motility, and connects to a digital monitor.

In a few years, technical development will allow us to routinely assess anxious patients with a battery of anxiety provocations while their physiological changes are being monitored by a portable system. This system could also prompt the patient to key in ratings for a variety of preprogrammed self-report items at specified times. It will also have information about the patients’ motor behavior, from which avoidant behavior can be registered. In other words, all three emotional response systems will be recorded. This monitoring can be extended to out-of-clinic situations and 24-h periods to assess activation during natural stress situations and during sleep. Afterwards, back in the clinic, computer programs will automatically score each channel, produce a printout of the physiological activation profile across different situations, and calculate several aggregate scores. Then the physiological activation profile of the individual can be compared to that of a reference control population and various patient populations, and the most reactive or most abnormal physiological systems can be identified. Such reference norms will be analogous to those developed for standard clinical questionnaires like the State-Trait Anxiety Inventory (Spielberger et al., 1970). The reason these norms do not yet exist is that psychophysiological devices were not widely available in the past. This will change over the next 10 years during which we anticipate a renaissance of clinical psychophysiology and biofeedback applications (see, for example, Wilhelm et al., 2000c).

The real challenge for establishing psychophysiological assessment in the clinic is in overcoming the insufficient conceptual understanding and database of individual-specific, situation-specific, and response-specific factors determining the quality and intensity of physiological concomitants of somatic symptoms in anxiety disorders. Systematic research will have to (1) develop standard testing protocols that will acquire diagnostic information efficiently by using the most potent and specific anxiety provocation for each anxiety disorder and physiologically distinct subgroup, (2) select the most relevant channels to be recorded, such as sympathetic measures like skin conductance, parasympathetic measures like respiratory sinus arrhythmia, respiratory measures like end-tidal PCO₂, and endocrine measures like salivary cortisol, (3) process each data source comprehensively to extract the most meaningful information, (4) integrate the multiple sources of information to gain a broad understanding of the physiological state of an individual in different anxiety situations, and (5) establish the reliability (on retest and between clinicians assessing the physiological response) of such an approach. Ideally, such physiological testing would meet psychometric standards comparable to those of currently accepted clinical assessment measures, but even if this is not achievable, the testing profile will be an important source of information to the patient and clinician complementing the information gained from self-reports of patients.

Such multimodal assessment is capable of detecting instances of clinically important decoupling of self-report from physiological measures. Decoupling is an example of where physiological assessment can add valuable information not available from self-report assessment. For example, Griffin et al. (1997) found that women rape victims who reported greater psychological dissociation (depersonalization) during the rape, had smaller heart rate increases when recounting their traumatic experience later than did women who reported less dissociation. Both groups, however, reported comparably high subjective distress while telling their story. Decoupling is hardly likely to be limited to Post-Traumatic Stress Disorder. Derealization or depersonalization is one of the 13 DSM-IV panic attack symptoms. This may be one reason that in some individuals, heart rate changes during panic attacks are small (Margraf et al., 1987). Another possibility is that in some individuals during some panic attacks, the physical symptoms experienced are 'phantom' symptoms, like the phantom pain and tactile or proprioceptive sensations experienced after removal of a limb. Central nervous representations of interoceptions may be activated during panic without actual involvement of peripheral nervous or endocrine systems. We observed decoupling of experience and physiology in our flight phobia patients (Wilhelm and Roth, 1997a): those given the tranquilizer alprazolam before a flight reported much less anxiety and fewer symptoms than the placebo group during flight, but in fact had higher heart and respiratory rates than the placebo group. The possibility of psychophysiological decoupling needs to be considered during diagnostic assessment and treatment. For example, in the case of dissociation with concomitant reduced general physiological activation, the best strategy may be to first help patients fully access trauma-related memories and get physiologically activated to support a more effective reprocessing ('emotional processing') of the trauma. Prior research (e.g. Lang et al., 1970) has

shown that anxious patients who show higher heart rates when imagining their feared situations at the beginning of treatment show better outcomes.

5. Conclusions

Although patients' reports of anxiety and of somatic symptoms such as sweating, pounding heart, and dyspnea are important to the assessment of DSM-IV anxiety disorders, physiological tests have yet to find a clinical role. In theory, physiology should provide information about anxiety complementary to that provided by speech and behavior. Appropriate physiological measures must show at least moderate concordance with self-reports and behavioral measures of an anxious state, providing converging evidence about its intensity and quality at different times. Some physiological measures may be trait-like, distinguishing subgroups of anxious patients from non-anxious controls regardless of how anxious the patients are at the moment. Finally, either state-like or trait-like physiological measures may distinguish a subgroup of anxiety patients with specific clinical characteristics, among which might be better or worse response to treatment.

Physiological assessment of anxiety is potentially important in at least three ways. First, it is a way to quantify anxiety symptoms. Second, it may be able to characterize the biological control mechanisms that are faulty in anxiety disorders. Disturbances at the hypothalamic level postulated by Gorman et al. (1989, 2000) to be present in Panic Disorder should be reflected in autonomic and respiratory measures. Third, it could provide evidence for characterizing specific types of anxiety and anxiety disorders. These could lead to more accurate assignment of patients to DSM-IV categories or be the basis for revised diagnostic categories or classification systems. The current flurry of research in biological psychiatry and psychology makes it likely that future diagnostic and treatment decisions will begin to be based on biological indicators of a biochemical, genetic, structural, and physiological nature. Managed health care demands 'hard' diagnostic data for treatment assignment and outcome assessment.

We propose using ambulatory physiological monitoring to detect activation disturbances in ecologically valid settings. Ambulatory monitoring is an important, expanding new technological development that up till now has been applied mainly to cardiovascular problems (electrocardiographic and blood pressure abnormalities) and epilepsy. The time is ripe for psychiatry to also benefit from this method. We envision a time when new patients complaining of anxiety and stress will routinely be monitored to complement their self-report in determining the severity and nature of their symptoms and what treatment is appropriate, and then will be monitored again during treatment to complement self-report data in evaluating its success. In the future, success of treatments could also be judged in terms of their ability to reverse abnormal physiological patterns. Our laboratory has developed software that is especially suited for the analysis of ambulatory

cardiovascular, electrodermal, and respiratory data (Wilhelm and Roth, 1996), and with some refinement, could be used in non-research clinical settings. Eventually how to apply this methodology and retrieve diagnostic information can be taught to clinical psychologists and psychiatrists. Involvement of manufacturers would be desirable to assist in the development of inexpensive and easy-to-use assessment systems.

In addition, portable biofeedback systems that target specific physiological systems to assist in anxiety treatment can be developed or are already available. For example, Grossman et al. (1985) describe a small portable monitor that provides paced breathing tones whenever the patient's respiratory rate (measured with a strain gauge) exceeds certain preprogrammed limits. The portable capnometer used in some of our studies can be programmed to beep when end-tidal PCO₂ or respiratory rate change beyond preprogrammed thresholds for longer than a specified period of time. In both devices, physiological measurements are stored in memory for later download and evaluation by the therapist or patient. Thus, ambulatory or portable physiological measuring devices have the potential of extending the therapeutic endeavors of psychologists and psychiatrists far beyond the confines of their consulting rooms.

Physiological recording is particularly relevant as an interface between psychiatry and general medicine. Anxiety, and panic disorder in particular, has recently emerged as a potentially important risk factor for coronary heart disease (CHD; Haines et al., 1987; Kawachi et al., 1994a,b; Kubzansky et al., 1997). Since six of the 13 diagnostic symptoms of a panic attack are also cardinal features of CHD, it is not surprising that PD is 30–50 times more common in noncardiac chest pain patients than it is in the overall population (Carter et al., 1994). In addition, the prevalence of PD in both cardiology outpatients and patients with documented CHD is high, ranging from 10–50%. The association between PD and CHD appears to be strongest in patients with atypical chest pain or symptoms that can not be fully explained by coronary status (Fleet et al., 2000). Studies of the mechanisms linking PD to CHD are still in their infancy, but there is preliminary evidence linking PD to reduced heart rate variability and temporal repolarization lability, two pathophysiological mechanisms related to CHD (Friedman and Thayer, 1998; Yeragani et al., 2000). It is also conceivable that anxiety-related hyperventilation induces coronary artery constriction (Rasmussen et al., 1986), which would increase the likelihood for cardiac episodes. Because many of the symptoms of PD mimic those of CHD, differentiating these disorders and learning how they may influence each other is imperative for clinical practice. Many unresolved issues leave our current understanding of the anxiety-health relationship incomplete.

Until now physiological testing in anxiety has been largely restricted to answering theoretical questions—the role of hyperventilation in anxiety attacks, the accuracy of interoception of bodily sensations, evidence for the suffocation false alarm hypothesis, or the localization of brain structures mediating anxiety (using fMRI or PET imaging; Nutt et al., 1999) for example. Typical experimental designs are to compare groups with and without pathology, each with about 15 members, and

look for statistically significant differences between them. We propose a paradigm shift towards clinical usefulness for health care professionals who interact with patients on a daily basis. That means perfecting physiological measures and provocations that alone or in combination are able not only to distinguish groups but to classify individuals in terms of anxiety states or traits and to determine the treatment outcome of an individual. Suitable state measures would show moderate to high concordance among the three response domains unless specific circumstances caused biases not common to all three. Our discussion of profiling introduced some of our ideas about the direction psychophysiological research should take to achieve clinical relevance.

Given the above evidence of respiratory dysregulation at least in a subgroup of PD patients, a convincing therapy of PD would have to show that these abnormalities are normalized as well. Although even very short cognitive-behavioral treatments for PD have been shown to be effective in terms of normalizing self-reported indicators of the disease (e.g. Clark et al., 1999), whether physiological measures would be normalized to the same degree has been ignored. The published success rates of cognitive-behavioral treatments are directly or indirectly based on self-reports, which easily could have been biased by the specific demand characteristics of this type of therapy or by nonspecific factors such as exaggerating distress to qualify for therapy, and minimizing distress at the end of therapy to please the therapist.

The current clinical practice of entirely neglecting physiological measurement in anxiety disorders when many of the defining symptoms are likely of physiological origin is paradoxical. Nevertheless, clinicians like Foa and Kozak (1998, see citation in Section 2) have every reason to be suspicious of psychophysicists bearing gifts. That skepticism may express itself in questions as to whether physiological anxiety measures possess the essential properties of a good test, such as reliability, validity, ease of administration, and unique contribution of information. In its original formulation, the three-systems approach was indifferent to whether a measure of anxiety would meet the requirement of classical test theory. Although the original assertion, that concordance between the three systems on such global variables as anxiety is necessarily low, was probably correct, objections based on this assertion have lost much of their relevance as clinical psychology and psychiatry have given up global concepts in favor of distinguishing between varieties of anxiety, anxiety disorders, and symptoms. In fact, as we have argued in this article, it is likely that — within specific behavioral test paradigms or from sophisticated ambulatory monitoring — single or combined measures with all the desirable test properties listed here can be established in the near future if research effort is directed towards that goal. The area of applied clinical psychophysiology has tremendous potential for development. Here we have discussed some issues that need to be resolved for this development to take place. We have presented some of our recent evidence of respiratory abnormalities in patients with panic disorder, which we think represents only the tip of the iceberg of clinically useful discoveries. But we also acknowledge that this is a challenging field — significant advances do not come easily.

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