Aversive Imagery in Panic Disorder: Agoraphobia Severity, Comorbidity, and Defensive Physiology

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Background: Panic is characterized as a disorder of interoceptive physiologic hyperarousal, secondary to persistent anticipation of panic attacks. The novel aim of this research was to investigate whether severity of agoraphobia within panic disorder covaries with the intensity of physiological reactions to imagery of panic attacks and other aversive scenarios.

Methods: A community sample of principal panic disorder ($n = 112$; 41 without agoraphobia, 71 with agoraphobia) and control ($n = 76$) participants imagined threatening and neutral events while acoustic startle probes were presented and the eye-blink response (orbicularis oculi) recorded. Changes in heart rate, skin conductance level, and facial expressivity were also measured.

Results: Overall, panic disorder patients exceeded control participants in startle reflex and heart rate during imagery of standard panic attack scenarios, concordant with more extreme ratings of aversion and emotional arousal. Accounting for the presence of agoraphobia revealed that both panic disorder with and without situational apprehension showed the pronounced heart rate increases during standard panic attack imagery observed for the sample as a whole. In contrast, startle potentiation to aversive imagery was more robust in those without versus with agoraphobia. Reflex diminution was most dramatic in those with the most pervasive agoraphobia, coincident with the most extreme levels of comorbid broad negative affectivity, disorder chronicity, and functional impairment.

Conclusions: Principal panic disorder may represent initial, heightened interoceptive fearfulness and concomitant defensive hyperactivity, which through progressive generalization of anticipatory anxiety ultimately transitions to a disorder of pervasive agoraphobic apprehension and avoidance, broad dysphoria, and compromised mobilization for defensive action.

Key Words: Agoraphobia, anhedonia, anxiety, anxiety sensitivity, chronicity, comorbidity, corrugator, depression, diagnostic subtypes, EMG, emotional reactivity, facial expressivity, heart rate, imagery, narrative imagery, panic, panic disorder, psychophysiology, skin conductance, skin conductance level (SCL), startle

Panic disorder is characterized by unexpected panic attacks and concern about their recurrence or injurious consequences (1), further specified by the presence or absence of agoraphobia—apprehension or avoidance of situations in which panic attacks are presumed likely. Although findings are mixed (2), panic disorder with agoraphobia is typically associated with more profound pathology (3), indexed in elevated apprehension about panic recurrence (4) and consequences (5), generalized symptomatology (e.g., nonspecific anxiety) (6), comorbidity (7–9), socio-occupational impairment (9,10), and poorer treatment outcome (11). Although reduced to a dichotomous distinction in the current nosology (DSM-IV), agoraphobia severity was previously qualified (none, mild, moderate, severe; DSM-III-R) (12) and contemporary investigations indicated a spectrum of increasing distress, least marked in panic disorder without agoraphobia and most marked in patients with severe situational avoidance (13). The current investigation of panic disorder examines whether the presence or absence as well as finer gradations of agoraphobia reflect differences in defensive reflex physiology during narrative imagery.

Script-driven emotional imagery is a valuable tool in studies of anxiety disorders, permitting presentation of both standard and idiographic threat challenges, paralleling methods of imaginal exposure therapy (14,15). Physiologic arousal during aversive imagery parallels anticipatory reactions to threatening events (16), similarly mobilizing the autonomic nervous system (e.g., heart rate, skin conductance), communicating threat through facial musculature (e.g., corrugator "frown" muscle), and prompting somatic reflexive action (e.g., startle potentiation) (17,18). Animals confronting survival threat show similar reactions, mediated by the brain's defense circuit (centered on the amygdala) (19,20) and neuroimaging studies suggest a comparable circuit (21–23) underlies human fear.

Whereas imagery has been a productive methodology for characterizing the physiology of posttraumatic stress disorder (PTSD) (24,25), a parallel database on panic disorder has yet to accumulate. In one of the first studies reported (26), panic patients relative to control participants showed elevations in blood pressure during idiographic aversive imagery, whereas other autonomic measures did not differ. In a subsequent study (27), sympathetic increases were modest in nocturnal, compared with diurnal, panickers during both standard aversive and neutral imagery, whereas facial expressivity and heart rate patterns were equivalent. Notably, in both studies—consistent with the vast majority of psychophysiological investigations (26–33)—patient groups were combined samples of panic disorder with and without agoraphobia. Although this grouping could be a constraint of sample size or an effort to accord with the International Classification of Diseases (ICD-10) (34,35), pathologically significant differences in emotional reflex patterns could be obscured.

In a series of imagery investigations, Lang and colleagues (17,36–44) explored evoked defensive arousal differences across anxiety disorders: specific and social phobia patients demonstrated the greatest autonomic and startle responses. Paradoxically, patients with more pervasive and diffuse anxiety symptomatology—generalized anxiety disorder (GAD), PTSD secondary to repeated traumatization—showed less robust reflex potentiation (despite reports of intense fear). Importantly, panic disorder with agoraphobia was located at the latter extreme. Furthermore, reflex blunting was consistently more pronounced across and within diagnoses, coincident with increased clinician-rated severity, poorer progno-

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sis, greater comorbidity (depression and anxiety), elevated questionnaire-based indexes of negative affectivity, and lengthier disorder chronicity, suggesting that defensive engagement during imagery might be compromised by prolonged hyperarousal, apprehension, and accompanying dysphoria (43,44).

In this study, a similar distress-related reflex pattern was expected within panic disorder. Similar to phobic disorders (36–43), panic patients without agoraphobia were expected to endorse the least symptomatic distress and show the most robust physiological reactivity (i.e., potentiated startle and enhanced autonomic and facial muscle action) during aversive imagery of panic attacks. Patients without agoraphobia and control participants were expected to react similarly during threatening imagery for which defensive mobilization is normal and adaptive (e.g., facing an attacking animal). In contrast, severe agoraphobia was expected to show higher comorbidity, broader negative affectivity, longer disorder duration, and, concomitantly, attenuated mobilization for defensive action.

Methods and Materials

Participants

Participants were assessed at the University of Florida Fear and Anxiety Disorders Clinic: 112 treatment-seeking adults with principal diagnoses of panic disorder without agoraphobia (PD; $n = 41$) and with agoraphobia (PDA; $n = 71$) and 76 healthy community control participants.

Diagnostic Classification

Diagnostic groups were established using the Anxiety Disorder Interview Schedule for DSM-IV (ADIS-IV) (45), a semistructured interview for assessing current anxiety, mood, substance use, and somatoform disorders and for screening psychosis and major physical disease.

For multiple Axis I disorders, diagnostic primacy was determined by clinician-rated severity (ranging from 0, No features present, to 5, Diagnosis present; severe) reflecting both distress and interference. Control participants denied current or lifetime diagnoses of psychiatric illness. Interrater reliability (via videotape) was calculated for 25% of patients, yielding 100% agreement for principal diagnosis among three masters- or doctoral-level clinicians.

The ADIS-IV enables assessment of agoraphobia extent by querying apprehension and avoidance of 22 standard situations (0, No avoidance/apprehension, to 8, Very severe avoidance/apprehension), specifically due to fears of panic induction and consequent difficulty escaping or securing assistance from others. In this study, presence of agoraphobia was defined as moderate to very severe apprehension or avoidance of at least two types of situations (i.e., transportation, shopping or recreational facilities, crowds, open spaces, being alone, enclosed spaces, work). Similar to preceding studies (2,3), agoraphobia without a history of panic disorder was rarely diagnosed ($n = 1$) in this sample and hence precluded analysis. Panic disorder patients with agoraphobia were further classified by a median split on the sum of their situational apprehension and avoidance ratings from the ADIS-IV, yielding 34 with moderate and 37 patients with severe agoraphobia. As an aside, although discussion continues concerning the diagnostic utility of agoraphobic avoidance versus distress (2–4), the 22 ratings of situational apprehension and avoidance were highly correlated in the current sample, $r = .92$, $p < .001$, and did not warrant separate analysis. Furthermore, convergent evidence that the defined groups reflected progressive increases in severity was observed in the agoraphobia subscale scores of the Fear Survey Schedule (46). (Relative to the control sample: PD, $z = 1.18$; panic disorder with moderate agoraphobia (PDA-moderate), $z = 3.54$; panic disorder with severe agoraphobia (PDA-severe), $z = 4.54$).

Procedure

The University of Florida Institutional Review Board (IRB-01) approved the study. Participants provided informed consent and completed questionnaires and an interview in the morning; psychophysiological assessment and clinical debriefing followed in the afternoon.

Experimental Stimuli. Twenty-four narrative imagery texts were used (47). Analyses focused on two idiographic, "personal" threat narratives representing each patient's primary clinical fear (i.e., panic attacks) or, for controls, their "worst fear" experiences (Table S1 in Supplement 1). Standard scenes included two panic attack (crowded checkout line, driving alone), four survival threat (physical attack by animal or human), two neutral (watching documentary, reading magazine) events. Filler scripts were low arousal or engaging pleasant scenes to impede an overall unpleasant arousal context. Scripts were approximately 20 words designed to reveal affect quickly and reflect active participation. A woman recorded the scenes using minimal prosody for presentation over earphones (Telephonics TDH-49, Telephonics, Huntington, New York).

Imagery Assessment. Seated in a quiet, dimly lit room with electrodes placed, participants were instructed to listen to the auditory scripts with eyes closed, vividly imagining the events described, as if actively involved. Throughout the recording session, soft tones cued participants to relax, breathe slowly, and silently repeat the word "one" to stabilize between-trial physiological activity (48). Imagery scripts were interspersed every 36 sec in the tone series, with content pseudo-randomized so that no more than two stimuli of the same hedonic valence (pleasant, neutral, unpleasant), or content category (e.g., survival threat) were presented consecutively. The script series was repeated in a counterbalanced order.

Trials consisted of a 1-sec baseline, a 6-sec auditory script, and 12 sec of imagery. Startle probes (50-msec 95 dB[A] white noise, instantaneous rise-time) were presented at 4 to 5.5 or 10 to 11.5 sec postscript onset, or both, and on 25% of intertrial intervals, at 22 to 23.5 sec postimagery offset.

Following imagery assessment (approximately 45 min) participants rated each scene for experienced pleasure and emotional arousal (49).

Experimental Control and Data Collection

A computer running VPM software (50) controlled stimulus presentation and data acquisition. Bioamplifiers recorded electromyograph (EMG) potentials at left orbicularis occuli and corrugator supercilii, skin conductance level (SCL), and electrocardiogram as reported previously (36).

Data Reduction and Analysis

Univariate analyses of variance (ANOVAs) and Tukey Honestly Significant Difference (HSD) tests for planned comparisons determined group differences in demographic and questionnaire data.

Using VPM software EMG, SCL [log[SCL + 1]], and electrocardiogram RR intervals (converted to beats per minute) were reduced into half-second bins. Responses were determined by subtracting amplitude during the 1 sec before script presentation from averages during the 12-sec imagery period.

Startle blinks from orbicularis oculi EMG represented the magnitude difference between onset and peak muscle potential (51), standardized within subject in relation to the mean and standard deviation of intertrial probe responses (36).