

Theoretical Review

SUBTYPES OF PANIC ATTACKS: A CRITICAL REVIEW OF THE EMPIRICAL LITERATURE

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Background: *Panic disorder is a heterogeneous disorder, comprising a variety of somatic, physiological, and cognitive symptoms during repeated panic attacks. As a result, considerable data have examined whether panic attacks may be classified into distinct diagnostic or functional subtypes. The aim of this study is to evaluate the existing literature regarding the validity of panic attack subtypes. Methods:* *This review focuses on data published since 2000, with the publication of DSM-IV-TR, augmented by replicated data published since 1980, with the publication of DSM-III and subsequently DSM-IV. Published reports evaluating empirical evidence for the validity of panic attack subtypes are reviewed. Results:* *Five sets of panic symptoms (respiratory, nocturnal, nonfearful, cognitive, and vestibular) have been shown to cluster together at varying degrees of consistency. However, none of these potential subtypes have been associated with sufficient and reliable external validation criteria indicative of functional differences. This apparent lack of findings may be related to methodological inconsistencies or limitations across the reviewed studies. Conclusions:* *Although at present the data do not warrant the utility of subtyping, further research aimed at patent gaps in the literature, including clearer operationalization of symptom subtypes, greater use of biological challenge paradigms and physiological and other more objective measures of fear and anxiety, and exploration of subtyping based on biological factors such as genetics, may support the future designation of panic attack subtypes and their ultimate clinical utility. Depression and Anxiety 26:878–887, 2009. © 2009 Wiley-Liss, Inc.*

Key words: *panic disorder; panic attacks; respiratory symptoms; nocturnal panic; nonfearful panic; cognitive symptoms; vestibular symptoms*

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INTRODUCTION

Over the past three decades, numerous researchers have investigated symptom subtypes of panic attacks. This is a logical, and potentially fruitful, area of inquiry. As defined in DSM-IV-TR, panic disorder is a relatively heterogeneous disorder, with its core feature, the experience of recurrent unexpected panic attacks, encompassing a variety of somatic, physiological, and cognitive symptoms that may vary across patients.^[1] If symptom clusters were to indicate distinct subtypes of panic attacks, and external validators (e.g., family history, co-morbidity, course, treatment response) were to suggest functional differences across the subtypes, clinical assessment and treatment procedures could be more effectively tailored to particular types of symptoms or patients. Although several authors have previously reviewed the literature on specific symptom clusters (e.g.,^[2,3]), no comprehensive review has been conducted. Additionally, no research has examined alternative approaches for subtyping panic attacks, such as genetics, which have emerged for other psychiatric disorders.^[4]

With these issues in mind, this review aimed to critically evaluate the existing literature regarding the validity of panic attack subtypes and areas in need of further study. The review focused on data published since 2000, with the publication of DSM-IV-TR, augmented by replicated data published since 1980, with the publication of DSM-III and subsequently DSM-IV. A PubMed search was conducted to capture published research across psychiatry, psychology, and related disciplines using the keywords panic attack subtypes, panic disorder subtypes, panic symptom subtypes, and panic symptom dimensions, which initially produced a list of 438 articles. This review was supplemented by a PubMed search using symptom-specific keywords and an inspection of bibliographies from key articles, which produced a list of 411 additional articles. These searches were then refined by restriction to articles written or translated into English and the inclusion of empirical evidence for the validity for panic attack subtypes.

EMPIRICAL LITERATURE

The literature search revealed data pertaining to five potential symptom subtypes (respiratory, nocturnal, nonfearful, cognitive, and vestibular). Table 1 summarizes the supportive findings. The reviewed studies varied widely in many respects, including sample size and composition, region and cultural factors, setting, and method of measuring panic symptoms, which may relate to their often divergent findings. Also of note, the available data were frequently restricted to subjective report and are thus considered provisional. None of the symptom sets were reliably associated with any demographic variables (e.g., gender, race, ethnicity,

socioeconomic status), thus these data are not reviewed herein.

RESPIRATORY SUBTYPE

Symptom profile. There is considerable evidence that the respiratory symptoms of panic attacks cluster together, although evidence for external validators is limited to self-report data. The respiratory subtype was first classified by Ley^[3] and expanded upon in Klein's^[5] suffocation false-alarm theory of panic. Currently, the respiratory subtype is operationalized as endorsement of four of the following five symptom criteria during an individual's most recent severe panic attack: feeling of choking or smothering sensations; shortness of breath; chest pain or discomfort; numbness or tingling sensations; and fear of dying. The nonrespiratory subtype is operationalized as that which does not meet these symptom criteria (e.g.,^[6-10]), thus representing a mixed group. Across nine recent studies conducted in clinics across various cultures, 30–65% met criteria for the respiratory subtype.^[6-8,10-15] However, the prevalence of this subtype has not been evaluated in epidemiological research.

Factor analytic studies of panic symptomatology have likewise reported strong associations among respiratory symptoms. Meuret et al.^[16] factor analyzed DSM-IV panic symptomatology in a sizeable clinical sample and arrived at a three-factor solution, with the first factor comprising "cardiorespiratory symptoms" of palpitations, shortness of breath or smothering sensations, feeling of choking, chest pain or discomfort, numbness or tingling sensations, and fear of dying. Similar factors have been obtained by others (e.g.,^[17-20]). Physiological challenge studies such as those involving CO₂ inhalation, hyperventilation, and breath-holding support these findings and may provide a more objective measure of panic attack symptomatology than self report. In three recent studies,^[8-10] patients diagnosed with panic disorder were classified into respiratory and nonrespiratory subtype groups and subsequently administered 35 or 65% CO₂/O₂ admixtures. In each of the studies, a significantly greater proportion of participants in the respiratory subtype group experienced a self-reported panic attack following CO₂ inhalation (63.3–93.7%) than did participants in the nonrespiratory subtype group (33.3–43.4%). Similar group differences were found in three studies using hyperventilation and breath-holding tasks.^[21-23] Notably, all six of these studies were conducted in the same laboratory and did not measure physiological responding. Additionally, several studies used small sample sizes or failed to report on sample composition (e.g., presence vs. absence of agoraphobia), potentially limiting their generalizability.

Family history. Several studies have found that the respiratory subtype is associated with greater familial history of panic disorder, although findings are limited to proband self report. Numerous studies indicate that

TABLE 1. Summary of current supportive evidence for validity of panic attack subtypes

Subtype	Evidence type	Evidence	Citation(s)
Respiratory	Family history	Greater history of panic disorder	7–9, 13, 21–26
		Greater history of any mental disorder	12, 22
	Comorbidity	Higher rates of respiratory problems	16, 19
		Higher rates of unipolar mood disorder	9, 21, 24, 30, 31; 12, 13
	Age of onset, course, clinical features	Earlier age of onset of panic disorder	7, 9, 24; 12, 13, 21–23
		Longer duration of panic disorder	14, 34
	Treatment response	Positive association with illness severity More rapid response to psychiatric medication	10, 14, 16; 36 12, 13; 15
Nocturnal	Family history	Greater history of any Axis I disorder	52
	Comorbidity	Positive association with depressive symptoms	37, 40, 43, 54–58; 39, 47, 48
		Positive association with anxiety symptoms	57, 58; 39, 47, 48
	Age of onset, course, clinical features	Longer duration of panic disorder	6, 53; 39
		Lower rates of agoraphobia Positive association with respiratory symptoms	6, 47; 40, 52 40; 39
Nonfearful	Comorbidity	Lower rates of agoraphobia	63, 64, 67, 68
		Lower rates of specific phobia	63, 68
		Lower rates of generalized anxiety disorder	64; 63
		Lower rates of major depressive disorder	62, 63; 64
	Age of onset, course, clinical features	Fewer physical symptoms of panic attacks Lower self-reported fear and/or anxiety	60, 63, 64, 67 60, 67
Cognitive	Treatment response	Less frequent psychiatric referral or treatment	62, 63, 67
	Comorbidity	Higher rates of Axis I disorders (when early-onset)	74
	Age of onset, course, clinical features	Fewer symptoms of panic disorder	75; 60, 61
Vestibular	Comorbidity	Positive association with depressive symptoms	81, 83
		Positive association with vestibular disorders	84, 85
	Age of onset, course, clinical features	Positive association with self-reported anxiety	79, 81
		Positive association with symptom severity	16
		Positive association with agoraphobic behavior Positive association with interference or impairment	88–90 16, 90

Note: Nonsignificant or opposing findings indicated in italics.

patients meeting criteria for the respiratory subtype^[7,8,13] or exhibiting strong respiratory symptoms during physiological challenge^[9,21–26] report a greater familial history of panic disorder, suggestive of greater familial loading for the respiratory than nonrespiratory subtype. In two studies, respiratory subtype patients reported greater familial history of any mental disorder.^[12,22] However, proband self report may be biased by possibly greater visibility of respiratory symptoms in the panic attacks of family members, relative to other panic symptoms. The few studies that have directly assessed first-degree relatives have produced inconsistent results.^[27,28]

Co-morbidity. The respiratory subtype has been associated with higher rates of co-morbid respiratory problems and possibly mood disorders. In two studies,^[16,29] panic disorder patients with predominant respiratory symptoms reported higher rates of co-morbid respiratory problems (e.g., asthma and bronchitis) than did participants without predominant respiratory symptoms, although these findings were not corroborated by medical reports. Goodwin et al.^[30] found an association between self-reported “shortness

of breath or difficulty breathing” and co-morbid dysthymia or depression, previously shown for dysthymia but not depression.^[31] Three studies measuring all five respiratory symptoms found a greater incidence of self-reported previous major depressive episodes for patients meeting respiratory subtype criteria or exhibiting a cluster of prominent respiratory symptoms,^[9,21,24] although two studies reported opposing findings.^[12,13] Thus, the data on co-morbidity of mood disorders are somewhat mixed, potentially related to methodological heterogeneity.

Age of onset, course, and clinical features. Findings regarding an association between respiratory symptoms and age of onset of panic disorder have been inconsistent, which may be related to the retrospective nature of participants’ self-reports. Several studies found an earlier age of onset,^[7,9,24] while others found a later age of onset^[12,13,21–23] for patients meeting respiratory subtype criteria or with predominant respiratory symptoms. Others have found variability among respiratory symptoms in relation to age of onset,^[32,33] which may help to explain the inconsistent findings. One recent study revealed longer duration of

illness for participants with predominant respiratory symptoms,^[14] previously shown by others.^[34] Several studies have demonstrated an association between the respiratory subtype or respiratory symptom clusters and higher scores on self- and clinician-rated measures of panic disorder severity,^[10,14,16] and moderate-to-severe levels of symptom severity.^[35] However, not all researchers have found such associations (see^[36]).

Treatment response. A very limited body of work suggests that respiratory symptoms may respond more rapidly than nonrespiratory symptoms to certain psychiatric medications. Studies using nortriptyline, a tricyclic antidepressant,^[12] and clonazepam, a benzodiazepine,^[13] found that the respiratory subtype exhibited greater improvement than the nonrespiratory subtype on self- and clinician-rated panic disorder severity measures at eight weeks of treatment, but similar rates of improvement at one year and at 12 weeks to three years of treatment, respectively. Neither of the studies employed a placebo control group, thus the results should be interpreted with caution. In one placebo-controlled clinical trial, clonazepam, a benzodiazepine, was found to be equally effective for the respiratory and nonrespiratory subtypes on similar severity measures at six weeks of treatment, although the cell sizes were relatively small.^[15]

NOCTURNAL PANIC SUBTYPE

Symptom profile. A distinct profile of symptoms defines nocturnal panic, although there is no consistent evidence for a nocturnal panic subtype of panic attacks based on external validators. A nocturnal panic attack is defined as an abrupt waking from sleep in a state of panic involving subjective fear or discomfort along with cognitive and physiological symptomatology similar to that during a diurnal panic attack.^[2,37] Diurnal panic attacks typically accompany nocturnal panic attacks,^[6,38–40] although a small subset of patients experience primarily nocturnal panic.^[41] Nocturnal panic attacks typically last approximately two to eight minutes and occur out of non-REM sleep. As reviewed by Craske and Tsao,^[2] nocturnal panic has not been reliably associated with any abnormalities in sleep architecture^[42–44] or electroencephalographic measures during sleep,^[42,43,45,46] and has been shown to be distinct from sleep disorders.

Nocturnal panic appears to be relatively common and interfering among panic disorder patients. In a large epidemiological study, an average of 58% (range = 44–71%) of participants with definite or probable panic disorder reported having experienced at least one nocturnal panic attack,^[41] and 30–45% of respondents reported recurrent nocturnal panic attacks (reviewed in^[2]). Furthermore, in a recent study with a clinical sample,^[47] recurrent nocturnal panic was reported to occur at an average of 11.4 attacks in the previous month. Nocturnal panic is often associated

with sleep problems such as difficulty returning to sleep and fear and avoidance of sleep, suggesting a specific contribution to distress and interference in functioning (reviewed in^[2,47,48]). Moreover, during other states involving loss of vigilance such as relaxation and hypnosis, patients reporting nocturnal and diurnal panic attacks exhibit reduced heart period variability as a more objective measure of dysregulated behavioral adaptation, relative to patients with diurnal-only panic attacks.^[49–51]

Family history. The small body of research examining the relation of nocturnal panic to familial psychiatric history has found no reliable association. Three studies utilizing self-report data for patients with nocturnal and diurnal panic and patients with diurnal-only panic^[40,52,53] found no group differences in history of panic disorder among first-degree relatives. However, one of the studies^[52] indicated a greater prevalence of at least one Axis I disorder among first-degree relatives, not specific to panic disorder.

Co-morbidity. There is mixed evidence regarding nocturnal panic and co-morbid psychiatric disorders. Two clinical studies reported greater lifetime rates of major depression^[54] and higher self-reported depressive symptomatology,^[40] respectively, among patients with nocturnal and diurnal panic relative to diurnal-only panic. These findings of a nocturnal panic-depressive symptom link are consistent with previous studies using both self-report and clinician data.^[37,43,55–58] Prior studies suggested higher rates of co-morbidity with anxiety disorders or self-reported anxiety difficulties in childhood in nocturnal and diurnal panic groups than diurnal-only panic groups (e.g.,^[57,58]), although these findings have not been replicated more recently. On the contrary, three studies found no differences with regard to co-morbidities of anxiety, mood, or any other mental disorders between the two groups.^[39,40,47,48]

Age of onset, course, and clinical features. Numerous recent studies have explored relationships between nocturnal panic and age of onset, duration of illness, stressful life events, agoraphobia, and respiratory symptoms. No consistent associations have been demonstrated, although some data may be influenced by difficulties in retrospective self report. Several studies found no association between presence of nocturnal panic and self-reported age of onset of panic disorder.^[39,40,52] Other research reported longer mean self-reported duration of panic disorder within nocturnal and diurnal panic groups relative to diurnal-only panic groups,^[6,53] although one study found no such association.^[39] Also, two of the studies found no differences in self-reported stressful life events between the two groups.^[40,52] Two studies demonstrated lower rates of agoraphobia in nocturnal plus diurnal panic groups than diurnal-only panic groups,^[6,47] although others found no differences.^[40,52] Similarly, findings for differential respiratory symptoms between the two groups are inconsistent.^[39,40]

Treatment response. No studies have examined differential effects of pharmacological or behavioral treatments between the two groups. Cognitive-behavioral therapy has been shown to significantly reduce frequency of nocturnal panic attacks,^[59] although no comparisons have been made between reductions in nocturnal and diurnal panic attacks.

NONFEARFUL AND COGNITIVE SUBTYPES

Based on the coupling vs. decoupling of physiological and cognitive components of panic attacks, several groups of researchers have proposed other subtypes of panic attacks: prototypic, cognitive, and nonfearful (e.g.,^[3,60,61]). Prototypic panic attacks involve high levels of physiological and subjective fear responding, exemplifying the general diagnostic criteria for a panic attack.^[1] Nonfearful and cognitive subtypes may be characterized by more specific symptom profiles.

NONFEARFUL SUBTYPE

Symptom profile. Nonfearful panic appears to be associated with two related external validators, although a clearer definition and more research is needed to warrant its utility as a subtype. Most commonly, the nonfearful subtype is operationalized as absence of endorsement of “fear of losing control or going crazy” or “fear of dying” symptom criteria, along with reported discomfort, but not fear, during the most recent severe panic attack.^[62] However, two recent physiological challenge studies in a panic disorder sample^[67] and a nonclinical sample,^[60] reliably classified the nonfearful subtype (11 and 32% of participants, respectively) on the basis of a more liberal definition involving high levels of physiological (e.g., cardiac and electrodermal) responding and low levels of self-reported distress during repeated panic attacks. Thus, a more consistent definition is needed.

Approximately 20–40% of panic attacks occur without reported cognitive symptoms of fear of losing control or going crazy or fear of dying,^[62,63] although these estimates may be influenced by recall bias, response biases, or poor insight. Researchers have argued that nonfearful panic may be particularly prevalent among medical patients,^[64] notably cardiology patients (e.g.,^[62,65–67]), and demand characteristics of presenting in a medical setting or seeking medical rather than psychological evaluation may also reduce self-report of cognitive symptoms. In two recent studies of nonfearful panic attacks in a cardiac medical setting^[67] and an emergency medical setting,^[64] 22 and 44% of patients meeting criteria for panic disorder, respectively, met criteria for nonfearful panic according to the more stringent definition above. Nonfearful panic appears to be associated with lower likelihood of referral for psychiatric treatment or medication,^[62,63,67] despite findings of no differences in functional impairment^[63] and rates of hospitalizations two years following initial admittance,^[64] relative to prototypic panic.

These data highlight the potential importance of nonfearful panic particularly within medical settings.

Family history. No recent studies have examined questions regarding nonfearful panic and familial psychiatric or medical history. One previous study found no differences between nonfearful and prototypic panic groups for panic disorder in first-degree relatives, based on a clinician-rated structured family history interview.^[66]

Co-morbidity. Most of the research suggests that nonfearful panic is associated with lower rates of psychiatric co-morbidity relative to prototypic panic. With regard to anxiety disorders, recent studies in both community and clinical samples found lower rates of co-morbidity with agoraphobia^[63,64,67] and specific phobia^[63] as previously found by others.^[68] Findings regarding co-morbidity with generalized anxiety disorder are inconsistent.^[63,64] With regard to mood disorders, a recent large-scale community study found lower rates of co-morbidity with major depressive disorder,^[63] as previously reviewed by others,^[62] although a study restricted to patients seeking medical attention for panic symptoms did not find this effect.^[64] This study also found no differences between nonfearful and prototypic panic groups in cardiac and chest pain diagnoses.^[64]

Age of onset, course, and clinical features. Despite findings that suggest no differences in age of onset, clinical severity, and functional impairment, nonfearful panic may be characterized by fewer physical symptoms of panic and lower scores on self-report measures of fear and anxiety. A recent study drawing from National Comorbidity Survey (NCS) data found no differences in self-reported age of onset of panic disorder between nonfearful and prototypic panic groups,^[63] shown earlier by others,^[68,69] although all three of these studies utilized DSM-III panic disorder criteria. Several recent studies reported no differences in intensity^[64] and frequency^[63,64] of panic attacks, functional impairment,^[63] or health-related quality of life^[67] between nonfearful and prototypic panic groups. However, in addition to fewer cognitive symptoms and lower levels of subjective fear and anxiety, nonfearful panic groups self-reported fewer physical symptoms relative to prototypic panic groups.^[60,63,64,67] Additionally, several studies demonstrated lower scores on other measures of fear and anxiety including trait anxiety and agoraphobic cognitions,^[67] body sensations,^[60,67] and anxiety sensitivity.^[60] At a two-year follow-up, one study indicated that some of these group differences diminished over time, suggesting a lack of differential improvement in nonfearful panic relative to prototypic panic.^[64]

Treatment response. No research has directly compared response to behavioral or pharmacological treatments in nonfearful vs. prototypic groups. As previously stated, nonfearful panic appears to be less likely to be referred for psychiatric treatment or to be treated with medication.^[62,63,67] Two previous studies

reported success with antipanic medication to reduce symptoms within nonfearful panic disorder.^[65,70]

COGNITIVE SUBTYPE

Symptom profile. The cognitive subtype of panic attacks has been relatively loosely characterized, and possibly consequently has not been reliably associated with any external validators. Based on the work of cognitive theorists (e.g.,^[71]), Ley's^[3] model of panic subtypes, and findings of physiological challenges studies,^[60,61] the cognitive subtype is generally operationalized as the presence of excessive fear or distress in the absence of measurable or elevated somatic or physiological responding during a panic attack. Two physiological challenge studies conducted in a panic disorder sample^[61] and nonclinical sample^[60] reliably classified the cognitive subtype (37 and 26% of participants, respectively) on the basis of low levels of physiological (e.g., cardiac and electrodermal) responding and high levels of self-reported distress during repeated panic attacks. However, operational definitions for the cognitive subtype have been inconsistent, and no clear symptom criteria have been widely accepted. As the presence of certain physical symptoms help to distinguish panic disorder from the other anxiety disorders, this subtype may be particularly elusive. No epidemiological studies have examined the prevalence of the cognitive subtype in clinical or community samples.

Several factor analyses of panic disorder symptomatology have demonstrated strong associations among cognitive symptoms. Meuret et al.'s^[16] factor analysis of DSM-IV panic symptomatology in a large clinical sample included a cognitive symptom factor comprising fear of losing control, fear of going crazy, and feeling of unreality. Similarly, Rucci et al.^[72] factor analyzed the 114-item lifetime Panic-Agoraphobic Spectrum self-report questionnaire and reported a "fear of losing control" factor comprising several items regarding fear of loss of cognitive control during panic attacks. Similar cognitive or "fear" factors have been obtained by others, although some factors included symptoms such as chest pain and paresthesias (e.g.,^[18,19,73]).

Family history. No studies have examined the relation of the cognitive subtype or predominant cognitive symptoms to family psychiatric history.

Co-morbidity. Only one study has examined associations between predominant cognitive symptoms of panic disorder and psychiatric co-morbidity. Utilizing NCS data, Goodwin and Hamilton^[74] found that early-onset panic (at or before age 20) with self-reported fear or anxiety upon the first panic attack was associated with higher rates of co-morbidity with various Axis I disorders, including anxiety disorders, major depressive disorder, bipolar disorder, and substance use disorders, and higher rates of suicidal ideation and attempts. Late-onset panic (after age 20)

with fear was also associated with higher rates of co-morbidity with agoraphobia, generalized anxiety disorder, and mania. However, retrospective reports of precise age of onset may have been biased by current symptomatology and require replication.

Age of onset, course, and clinical features. Only a handful of studies have investigated age of onset, course, or clinical features of panic disorder based on the cognitive subtype, and findings have been inconsistent. In two physiological challenge studies,^[60,61] the cognitive subtype was similar to the prototypic subtype in subjective fear and anxiety during panic attacks, although findings regarding cognitive symptoms, somatic symptoms, physiological responding, and overall symptom severity were conflicting. One study using self-report data^[75] found that fewer DSM-IV symptoms of panic disorder were endorsed by patients fitting criteria for the cognitive subtype.

Treatment response. No studies have examined the relation of the cognitive subtype or predominant cognitive symptoms to response to behavioral or pharmacological treatments for panic disorder.

VESTIBULAR SUBTYPE

Symptom profile. A clear vestibular subtype has not been identified either on the basis of a set of symptoms or external validators. Currently, the vestibular subtype is generally characterized by the experience of dizziness during and between panic attacks, and possibly abnormalities in vestibular or balance functioning as assessed by a variety of tests (e.g., electro-nystagmography, posturography, and rotational). Early work by Jacob et al. (e.g.,^[76,77]) explored relationships between panic attacks and vestibular functioning by conducting standardized ontoneurologic testing with panic disorder and healthy control groups. In general, this research group (e.g.,^[78]) and others (e.g.,^[79]) found evidence for significantly elevated vestibular abnormalities in panic disorder groups compared to controls (75 and 71% of patients, respectively), although some of the groups were preselected on the basis of vestibular complaints. Similar group differences were recently reported within patient samples that were not preselected for dizziness symptoms.^[80,81]

Approximately 50–85% of patients with panic disorder report the experience of dizziness during panic attacks,^[82] relatively consistent with Jacob and colleagues' more objective findings for vestibular abnormalities^[78–81] and supportive of the symptom's high frequency. Meuret et al.'s^[16] factor analysis of DSM-IV panic symptomatology in a sizeable clinical sample indicated a "mixed somatic" factor comprised of symptoms of dizziness, nausea, trembling, sweating, and chills/hot flashes, and a prior analysis^[20] also obtained a vestibular symptom factor. However, it appears that dizziness between panic attacks, rather than during panic attacks, may serve as better predictor of vestibular abnormalities in panic disorder

patients^[77,81] although not all researchers have found this effect (see^[80]).

Family history. No recent studies have explored the relationship between vestibular symptomatology and familial psychiatric or medical history.

Co-morbidity. Very few studies have examined relationships between vestibular symptomatology and psychiatric co-morbidity. One recent study demonstrated an association between vestibular dysfunction in panic disorder patients and elevations in self-reported depressive symptoms.^[81] Likewise, a previous study within a non-panic disorder outpatient sample found an association between self-reported persistent dizziness and lifetime and current major depression and dysthymia.^[83] There also appears to be some overlap between vestibular symptoms in panic disorder and diagnosis of vestibular disorders (reviewed in^[84,85]).

Age of onset, course, and clinical features. Although age of onset and course of panic disorder have not been examined, there is some evidence that vestibular symptomatology or vestibular abnormalities may be associated with higher levels of subjective anxiety, clinical severity, and agoraphobia in panic disorder patients. Tecer et al.^[87] tested patients with panic disorder for vestibular dysfunction using electronystagmography (ENG), and found that patients with ENG abnormalities showed higher scores on self-report measures of trait anxiety than patients without abnormal ENG results. These findings are consistent with a prior study.^[79] Meuret et al.^[16] observed that dizziness was self-reported as one of the most severe panic symptoms within a patient sample. Previous studies also demonstrated associations between dizziness symptoms and catastrophic cognitions such as fear of losing control, fainting, or dying.^[86,87] As reviewed by Vaillancourt and Bélanger^[88] and reported by Yardley et al.,^[89,90] panic symptomatology characterized by predominant dizziness may be associated with higher rates of self-reported agoraphobic behavior. Last, two studies suggested that dizziness symptoms,^[90] and mixed somatic symptoms^[16] respectively, may be related to interference or occupational impairment in daily life.

Treatment response. No studies have examined the relation of vestibular symptomatology or vestibular functioning to response to behavioral or pharmacological treatments for panic disorder.

CONCLUSIONS

Overall, the extant data do not provide strong support for any of the potential symptom subtypes of panic attacks reviewed herein. As indicated, each set of symptoms has been shown to cluster together and/or comprise a subgroup of patients with panic disorder, providing initial support for research investigating subtypes. Notably, however, none of the sets of surface symptoms or behavioral descriptors have been associated with reliable and sufficient external validation

data needed to distinguish them from other symptoms and thus warrant the clinical utility of subtyping.

Indications of symptom subtypes would first require future research to utilize consistent criteria to define symptom-based groups, particularly for nonfearful, cognitive, and vestibular symptom groups, for which current definitions have been shown to be inconsistent and unclear. Studies in this area have also varied widely in their methodology and other central characteristics, which may relate to their often divergent findings. As a more general weakness, the available data have been frequently limited to patient self report of symptoms, which as noted may be influenced by several types of biases. Taken together, these various inconsistencies and limitations create challenges for finding any meaningful group differences. Future research should explore group differences across a wider range of measures, including psychophysiology and actual behavior, which have been inadequately explored in the literature thus far. For example, although physiological challenge paradigms have often used self-reported symptomatology as a dependent measure, these studies have the capacity to elicit more objective and concurrent measures of fear and anxiety.

As another potential limitation of the data, a small body of longitudinal research on within-individual panic symptomatology^[91,92] indicates that patients self-report a variety of symptom patterns over the course of illness, with the exception of nocturnal panic that has not been studied in this manner. More careful longitudinal study is needed to reconcile these findings with aforementioned reports of within-individual reliability of symptom subtypes under conditions of physiological challenge (e.g.,^[23,24,60,61]).

Finally, it is likely that panic syndromes may cluster by underlying biological factors, such as genetics, rather than similarity in symptoms, which will be an important area for future research on panic disorder as with other psychiatric disorders, particularly considering limitations in the data on symptom subtypes. For example, genetics research has demonstrated that multiple genes may produce the same observable phenotype or "symptoms" (genetic heterogeneity) and the same genetic variants may produce multiple phenotypes (phenotypic heterogeneity).^[4] Discernible endophenotypes as alternatives to symptom subtypes in anxiety disorders may be derived from animal models, brain circuitry, and stress responding, possibly in interaction with environmental events such as physiological challenge.^[93]

Although the reviewed data do not support the designation of any symptom sets as panic attack subtypes, these data may be used to indicate the heterogeneity of panic disorder symptoms as presented across a variety of clinical, medical, and community settings, and their frequent departure from prototypic panic attacks while retaining the core syndromal features of recurrence, unexpectedness, and associated discomfort and/or distress.

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