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SPECIAL ARTICLE

Panic disorder respiratory subtype: psychopathology and challenge tests – an update

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Panic disorder (PD) pathophysiology is very heterogeneous, and the discrimination of distinct subtypes could be very useful. A subtype based on respiratory symptoms is known to constitute a specific subgroup. However, evidence to support the respiratory subtype (RS) as a distinct subgroup of PD with a well-defined phenotype remains controversial. Studies have focused on characterization of the RS based on symptoms and response to CO_2. In this line, we described clinical and biological aspects focused on symptomatology and CO_2 challenge tests in PD RS. The main symptoms that characterize RS are dyspnea (shortness of breath) and a choking sensation. Moreover, patients with the RS tended to be more responsive to CO_2 challenge tests, which triggered more panic attacks in this subgroup. Future studies should focus on discriminating respiratory-related clusters and exploring psychophysiological and neuroimaging outcomes in order to provide robust evidence to confirm RS as a distinct subtype of PD.

Keywords: Panic disorder; panic attacks; carbon dioxide; respiration; dyspnea; symptoms

Introduction

Patients with panic disorder (PD) experience recurrent panic attacks (PA), which are characterized by sudden, unexpected episodes of intense fear and/or discomfort. According to the DSM-5 definition, a PA is characterized by at least four of 13 possible signs or symptoms. These include somatic, physical, and cognitive aspects, such as palpitations, sweating, trembling, shortness of breath, choking, chest pain or discomfort, nausea, dizziness, chills or hot flashes, paresthesia or numbness, depersonalization (feeling detached from oneself)/derealization, fear of losing control/going crazy, or fear of dying.[1]

Besides acute PAs, anticipatory anxiety and avoidance behavior are also frequent manifestations of PD.[2] Therefore, the clinical presentation of PD can be very heterogeneous, which hinders disease management and compromises research outcomes.[3]

In an attempt to address this heterogeneity, distinct clusters of PD have been proposed on the basis of the predominant signs and symptoms,: 1) respiratory; 2) nocturnal; 3) nonfearful; 4) cognitive; and 5) vestibular.[4] After many efforts to identify PD subtypes, respiratory symptoms seem to be the best markers to classify PD patients into clusters.[5-7]

The link between PD and the respiratory system has been explored in several studies.[8-10] Respiratory abnormalities are common in patients with PD.[11-15] Resting subjects with PD present high minute ventilation, low CO_2 concentration in expired air, and an irregular breathing pattern.[16] These abnormalities of respiratory function are considered a vulnerability factor for PAs and seem to be specific to PD; they are not present in other anxiety disorders, such as social phobia and generalized anxiety disorder.[17,18]

Psychophysiological responses can also confirm the link between PD and respiration when patients are subjected to respiratory challenge tests.[19] Inhalation of elevated CO_2 concentrations, voluntary hyperventilation, and other methods to trigger acid-base disturbances, such as sodium lactate infusion, can induce similar panicogenic symptoms in some patients with PD.[20-25] Moreover, a bidirectional relationship between PD and pulmonary disorders – particularly chronic obstructive pulmonary disease and asthma – has been observed, reinforcing this link.[26-28]

Briggs et al.[29] suggested two subgroups of PD, the respiratory (RS) and nonrespiratory (NRS) subtypes, based on the presence or absence of respiratory symptoms. Criteria for the RS require the presence of at least four of five respiratory-related symptoms: breathlessness, chest pain, choking, fear of dying, and paresthesia.[29] (Hyperventilation episodes reduce CO_2 levels in the blood, leading to respiratory alkalosis and culminating in

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paresthesia or numbness.) Briggs et al. also identified differences in response to pharmacotherapy between the RS and non-RS subgroups.[29]

The respiratory cluster can be a valid means of distinguishing a PD subgroup with a specific clinical course and distinct response to treatment and challenge tests.[29-31] Moreover, the use of categories can help guide clinical assessment and therapeutic approaches, as well as provide optimal methodological strategies for research. However, whether the RS can be recognized as a distinct subgroup of PD with a well-defined phenotype remains controversial. Our group has summarized psychopathology-related findings and other aspects to characterize this subtype elsewhere.[30,32,33] In this context, the objective of this review rests on the contribution of recent findings about the respiratory PD subtype and focuses on its validity in clinical practice and research, considering both clinical phenotype (signs and symptoms) and biological profile (CO_2 sensitivity).

Epidemiology

Clusters associated with respiratory symptoms have characterized more than 50% of the overall sample in several studies of PD. In one group of 193 PD patients, 56.5% (n=109) were classified as having RS according to Briggs et al.'s criteria.[29,34] In another sample of 124 subjects, 63.7% (n=79) met the same RS criteria.[35]

PD was diagnosed in 431 subjects in a U.S. data survey of the general population (n=8,098). The presence of dyspnea during PAs discriminated a subtype that displayed increased odds of other panic symptoms associated with breathing, such as choking, chest pain, dizziness, and fear of dying, which accounted for 50.1% (n=216) of cases.[36]

In a sample of 8,796 individuals from six European countries, 2,257 were found to experience PAs. Participants were classified as having respiratory or nonrespiratory PA depending on whether PA was associated with shortness of breath. Among subjects with PA, the respiratory group represented 70% of cases, and was associated with increased health services utilization. The lifetime prevalence of respiratory PAs was 6.77% (3.14% in the nonrespiratory group), while the 12-month prevalence was 2.26% (1% in the nonrespiratory group).[37]

Roberson-Nay & Kendler[6] described two distinct classes of PD: class 1, represented by subjects with respiratory-dominant symptoms, and class 2, comprising individuals with more somatic symptoms and few respiratory signs. Using a different exploratory analysis approach and distinct datasets, approximately 56% of subjects (n= 2,390) were found to belong to class 1.[6]

Analysis of PD clusters

The existence of PD subtypes was first suggested by Klein, who, based on the "suffocation false alarm theory," proposed a subgroup of PD patients experiencing mainly respiratory signs and symptoms.[38] Briggs et al.[29] subsequently pioneered the evidence-based discrimination of PD subgroups, as described above.

According to the neuroanatomical hypothesis of Gorman et al.,[39] PAs originate from a dysfunction in the fear network of the brain, that integrates various structures of the brainstem, amygdala, medial hypothalamus, and cortical regions. The serotoninergic (5-HT) system is well positioned to influence these areas, with neuronal cell bodies in the brainstem raphe nuclei and widespread axonal projections to the forebrain regions.[40] In patients with symptomatic PD, studies have demonstrated decreases in midbrain 5-HTT and 5-HT1A receptor binding. This could reflect a compensatory process attempting to increase 5-HT neurotransmission, particularly in the dorsal periaqueductal gray-amygdala pathway, in order to inhibit hyperactivity or spontaneous neuronal discharge in this region.[41] In addition, patients with PD have dysfunction of the GABAA receptors and/or altered brain GABA concentrations. Accordingly, PD has been treated primarily with drugs that have anxiolytic properties, including benzodiazepines, which increase the potency of GABA by modulating the function of GABAA receptors, and selective serotonin reuptake inhibitors (SSRIs), which increase synaptic availability of 5-HT by blocking its transport into neurons.[42] Interestingly, patients with the RS experience a greater number of spontaneous PAs and respond better to antidepressants, whereas those with the NRS experience more situational PAs and respond more efficaciously to benzodiazepines.[29]

Since the first description of the RS in 1993, other different approaches have sought to identify PD clusters.[29] Cox et al.[43] identified a three-factor structure based on 23 signs and symptoms described in the DSM-III and in the Panic Attack Questionnaire: cluster 1 would correspond to dizziness-related symptoms, such as paresthesia; cluster 2 would represent the cardiorespiratory distress subgroup, who mainly experience tachycardia, dyspnea, choking, chest pain, and fear of dying; and cluster 3 would be associated with cognitive factors (fear of going crazy or fear of losing control).[43]

Using a similar analytical method, but a set of 13 PD signs and symptoms, a sample of 330 PD patients from six different countries was assessed. Subjects reporting four or more of these signs and symptoms (mainly fear of dying, chest pain/discomfort, dyspnea, numbness, and choking; n=163) tended to develop spontaneous PAs more frequently than those patients with fewer symptoms.[44]

In a Japanese sample (n=207), 15 clinical signs and symptoms (13 main symptoms including agoraphobia and anticipatory anxiety) were evaluated as present or absent. A principal component factor analysis revealed three clusters: cluster A comprised dyspnea, sweating, choking, nausea, and flushes/chills; cluster B included dizziness, palpitations, trembling or shaking, depersonalization, agoraphobia, and anticipatory anxiety; and cluster C encompassed paresthesia, chest pain, fear of dying, and fear of going crazy.[45]

Rees et al.[46] performed a principal component analysis based on 11 symptoms, which were rated by a sample of 153 PD patients on a scale of 0 to 4 (not present, mild, moderate, severe, and very severe). The analysis detected five clusters: 1) shortness of breath and choking sensations, which seem to represent respiratory difficulty;

2) dizziness and depersonalization; 3) nausea, sweating, and flushing; 4) two groups of cardiovascular signs and symptoms, palpitations, and trembling; and 5) chest pain and numbness. According to this analysis, the component that explained the greatest proportion of variance among clusters was the class of respiratory symptoms (shortness of breath and choking sensation).[46]

Segui et al.[47] also found three clusters, which they termed cardiorespiratory, vestibular, and general arousal. The cardiorespiratory cluster, which included the signs and symptoms palpitations, fear of dying, chest pain, paresthesia, trembling, and dyspnea, was the most representative one (26.1% variance).[47] In two other studies,[48,49] the symptoms of dyspnea and choking were grouped together in a respiratory cluster. However, in both studies, this subtype accounted for a lower percentage of variance than the other clusters.[48,49]

In an exploratory analysis factor with 343 PD patients, each of the 13 symptoms that can occur during a PA was rated on a qualitative scale of 0 to 8 (absent to very severe). Based on the scores of these symptoms, three subtypes could be discriminated: cardiorespiratory, autonomic/somatic, and cognitive (18.8, 6.4, and 3.8% of variance, respectively). The symptoms most strongly associated with the cardiorespiratory subtype were palpitation, shortness of breath, choking, chest pain, fear of dying, and numbness. The predominant signs and symptoms in the autonomic/somatic variety were sweating, trembling, nausea, chills/hot flushes, and dizziness. Finally, the cognitive type reported feelings of unreality, fear of going crazy, and fear of losing control.[5]

Two studies evaluated possible subgroups in Turkish patients with PD.[50,51] Sarp et al.[50] found that three factors – respiratory-circulatory, cognitive, and autonomic – explained 34.3, 16.5, and 10.8% of total variance, respectively.[21] In 159 PD subjects, Konkan et al. found evidence for a five-factor model, distributed across autonomic (15% variance explained), vestibular (9.38%), cardiovascular (8.89%), pseudoneurologic (7.95%), respiratory (7.5%), and fear-of-dying (7.1%) signs and symptoms.[51] As described in Table 1, the number of symptoms considered and the rating method employed in the analysis might explain the differences among these studies.

Roberson-Nay[6] screened subjects from four epidemiological datasets and one clinical trial (total = 4,268 PD subjects). Each database was examined separately, according to different statistical approaches. Four databases fit better into a two-cluster model (cluster 1 corresponding to major respiratory signs and symptoms such as dyspnea, chest pain, choking, paresthesia, and fear of dying). One database revealed three distinct clusters (high respiratory and somatic symptoms, milder respiratory symptoms, and low respiratory and high somatic symptoms) (Table 1).[6] The same authors compared several external validators (temporal stability, psychiatric comorbidity, and treatment response) between the RS and NRS, classified according to their own criteria.[6] They found a higher prevalence of major depression and other anxiety disorders in patients with the RS, as well as a higher utilization of pharmacological and psychological treatment than in NRS subjects.[7]

PD clusters were explored in a recent study[3] which employed anxiety markers based on Beck Anxiety Index (BAI) scores. A sample of 658 PD patients was divided into three classes: cognitive-autonomic subtype (n=196, 29.8%), with predominance of cognitive symptoms; autonomic subtype (n=197, 29.9%), with milder respiratory and cognitive signs; and a specific subtype, characterized by mild autonomic signs and absence of clear dimensions. For the autonomic class, the authors considered feeling of choking and difficult to breathing as respiratory symptoms and feeling hot, nausea, and flushes as autonomic symptoms. All anxiety markers were highest in the cognitive-autonomic subtype, with dyspnea, feeling of choking, and fear of dying as the predominant symptoms.[3]

In summary, there is a trend to recognize respiration-related signs and symptoms as good markers to discriminate among distinct subtypes of PD. In this context, the assessment of PA signs and symptoms could be very useful to identify subgroups and, consequently, allow more accurate data analyses and better interpretation of results. Special care must be taken to identify analysis-linked putative biases, such as number and type of symptoms, and the best method to rank them. Taken together, these findings are indicative a respiratory subtype group represented by diverse cardiorespiratory manifestations.

In the face of these controversies, Drenckhan et al.,[52] in a differential analytical approach, divided physical and psychological PA symptoms to discriminate a "pure" respiratory cluster, resulting in separate dimensions of cardiac, respiratory, and vestibular/mixed somatic factor. Shortness of breath and choking were the main symptoms representing the respiratory factor.[52] Indeed, these symptoms were included in the respiratory cluster in all studies,[5,7,43-52] except that of Segui et al.[47] Table 1 shows the main findings related to the aforementioned studies, while Table 2 lists the sign-and-symptom profile of the cluster most representative of respiratory-related symptoms.

Clinical characterization

Controversy remains regarding the expression of distinct clinical features between respiratory-related and nonrespiratory clusters. Freire et al.[25] and Song et al.[53] found a lower age of onset among RS compared to NRS patients (27.0 ± 7.9 vs. 31.1 ± 9.1 years, $p = 0.016$ and 35.4 ± 10.5 vs. 41.5 ± 9.1 years, $p = 0.04$, in Freire et al.[25] and Song et al.,[53] respectively). However, no differences were observed in other studies.[7,54-56] Biber & Alkin[54] found a longer duration of disease in the RS (50.8 ± 60.7 vs. 23.1 ± 23.5 months, $p < 0.05$), but this outcome was not found by others.[53,55] A family history of mental disorders was more prevalent in RS patients in several studies.[25,57,58] Demographic data, such as gender, age, occupation, education, and marital status, are consistently similar across the two groups.[6,25,56-58]

In one study, the presence of comorbidities, such as agoraphobia, major depression, and other anxiety disorders, was higher in RS groups, as was increased utilization of psychological and pharmacological treatments.[7] In another study, the incidence of agoraphobia, fear of respiratory manifestations, and number of PA symptoms were all higher

Table 1 Main findings of studies focusing PD clusters

Study	Year	Sample size	Symptoms considered for analysis	Rating scale	Statistical procedures	Clusters based on symptoms (or symptom profile of clusters)
Briggs[29]	1993	1,168	14 (based on DSM-III-R, faintness, and dizziness independently)	Presence or absence	PCA	**Subtype of presence of prominent respiratory symptoms – 1, 2, 3, 4, 5** Subtype of absence of prominent respiratory symptoms – 6, 7, 8, 9, 10
Cox[43]	1994	212	23 (based on Panic Attack Questionnaire)	0-4 (not present, mild, moderate, severe, very severe)	PCA	Dizziness-related symptoms (28.2% of variance) – 5, 7, 11 (hyperventilation-related symptoms) **Cardiorespiratory distress (9.9%) – 1, 2, 3, 4, 6** Cognitive factors (8.7%) – 12
Bandelow[44]	1996	330	13 (DSM-III-R)	Presence or absence	PCA	**Cardiorespiratory cluster (60.6% of sample) – 1, 2, 3, 4, 5** Cluster 2 (39.4%) – 6, 8, 9, 12, 13
Shioiri[45]	1996	207	15 (13 DSM-III-R, agoraphobia and anticipatory anxiety included)	Presence or absence	PCA	**Cluster A – respiratory cluster (9.5% of variance) – 1, 2, 8, 10, 13** Cluster B (10.9%) – 7, 6, 9, 14, 15, 16 Cluster C (9.5%) – 5, 4, 3, 12
Rees[46]	1998	153	11 (DSM-III-R and DSM-IV) – fear of dying, fear of going crazy, and losing control not included	0-4 (not present, mild, moderate, severe, very severe)	PCA	**Cluster 1: 1, 2 (27.7%)** Cluster 2: 7, 14 (12.6%) Cluster 3: 8, 10, 13 (9.7%) Cluster 4: 6, 9 (9%) Cluster 5: 4, 5 (8.3%)
Segui[47]	1998	274	14 (DSM-III-R, faintness, and dizziness independently)	0-3 (non-existent, mild, moderate, severe)	PCA	**Cardiorespiratory (26.1% variance) – 1, 4, 5, 6, 9** Vestibular (15.1%) – 7, 11, 12 Mixed (8.5%) – 2, 8, 10, 14 General arousal (7.2%) – 5, 8, 9, 13
Neerakal[48]	2002	94	13 (DSM-IV-TR)	Presence or absence	PCA	Autonomic (17.8% of variance) – 8, 9, 10 Cognitive (12.8%) – 12, 14 Mixed (10.75%) – 5, 13, 4, 3 **Respiratory (8.7%) – 1, 2**
Meuret[5]	2006	343	14 (DSM-IV)	0-8 (none to very severe)	EFA	**Cardiorespiratory (18.8% variance) – 1, 2, 3, 4, 5, 6** Autonomic/somatic (6.4%) – 7, 8, 9, 10, 13 Cognitive (3.8%) – 15, 12
Sarp[50]	2010	105	13 (DSM-IV-TR) + 7 further symptoms	0-3 (none to severe)	PCA	**Respiratory-circulatory (34.3% of variance) – 1, 2, 3, 4, 5, 6** Cognitive (16.5%) – 12, 14 Autonomic (10.8%) – 7, 9, 10, 13

Continued on next page

Table 1 (*continued*)

Study	Year	Sample size	Symptoms considered for analysis	Rating scale	Statistical procedures	Clusters based on symptoms (or symptom profile of clusters)
Roberson-Nay[7]	2012	NESARC (2,294) ECA (351) VATSPSUD (102) CNCPS (1161) NCS (360)	11 symptoms (CA) 13 symptoms (other databases)	Presence or absence	FMM EFA LCA	CNCPS (**class 1 [64.5% of sample] – 1, 2, 3, 4, 5** and class 2 [35.5%]) – lower endorsement of 12, 13, 14 ECA (**class 1 [54.5% of sample] – 1, 2, 4, 5, 7** and class 2 [45.5%]) – 6, 8, 9, 10 NCS (**class 1 [53.2% of sample] – 1, 2, 3, 4, 5** and class 2 [46.8%]) – lower endorsement of 2, 3, 5 VATSPSUD (**class 1 [50.1% of sample] – 1, 2, 3, 4, 5** and class 2 [49.9%]) – 6, 9, 10 NESARC – **high respiratory and somatic symptoms (38.1%) – high all 13 symptoms, milder respiratory class (27.3%) – 1, 3, 4, 6, 7**; low respiratory and high somatic symptoms (34.7%) – 6, 8, 9, 10
Konkan[51]	2013	159	13 (DSM-IV-TR) + fear of stroke + desire to escape	Presence or absence	PCA	Autonomic activation (15% of variance) – 8, 10, 12, 13 Vestibular symptoms (9.3%) – 7, 9, 14 Cardiovascular symptoms (8.8%) – 4, 6 Pseudoneurologic symptoms (7.9%) – 1, 5, 17 **Respiratory system (7.5%) – 1, 2, 12, 13** Fear of death (7.1%) – 3, 13, 18
Pattyn[3]	2015	658	Beck Anxiety Index (21-item)*	1 = notat all; 2 = mild; 3 = moderate; 4 = severe.Absence = 1/2, presence = 3/4	FMM EFA LCA	**Cognitive-autonomic subtype (29.8% of sample) – 1, 2, 3, 6, 12 + being scared and fear of the worst happening** Autonomic subtype (29.9%) – low respiratory and cognitive items Specific subtype (40.3%) – low autonomic item probabilities and absence of clear dimensions
Drenckhan[52]	2015	369	10 (DSM-IV-TR) with no cognitive symptoms (items 3, 12, 14)	0-4	CFA in different dimensional models	Cardiac – 4,6 **Respiratory – 1, 2** Vestibular/mixed somatic factor – 5, 7, 8, 9, 10, 13
Bruno[49]	2018	74	13 (DSM-IV-TR)	Not described	PCA	Somatic dissociative (18.3% of variance) – 7, 9, 12, 14 **Respiratory (13.7%) – 1, 2** Cardiologic (12.7%) – 3, 4, 6

Bold clusters show the most representative respiratory symptoms. Symptoms: 1 = shortness of breath/dyspnea; 2 = choking/smothering; 3 = fear of death; 4 = chest pain; 5 = tingling/numbness/paresthesias; 6 = palpitations/tachycardia; 7 = dizziness; 8 = flushes/chills; 9 = trembling/shaking; 10 = sweating; 11 = faintness; 12 = fear of going crazy/losing control; 13 = nausea/abdominal discomfort; 14 = depersonalization/derealization; 15 = agoraphobia; 16 = anticipatory anxiety; 17 = fear of stroke; 18 = desire to escape.
CFA = confirmatory factor analysis; CNCPS = clinical trial for PD; ECA = epidemiologic catchment area; EFA = exploratory factor analysis; FMM = factor mixture modeling; LCA = latent class analysis; NCS = National Comorbidity Study; NESARC = National Epidemiologic Survey on Alcohol and Related Conditions; PCA = principal component analysis; PD = panic disorder; VATSPSUD = Virginia Adult Twin Study of Psychiatric and Substance Use Disorders.
* Items added: being unable to relax, feeling terrified, nervous, scared, and fear of worst happening.

Table 2 Symptom profile of the cluster more representative of respiratory symptoms in each study

Symptoms	Briggs[29]	Cox[43]	Bandelow[44]	Shioiri[45]	Rees[46]	Segui[47]	Neerakal[48]	Meuret[5]	Sarp[50]	Roberson-Nay[7]	Konkan[51]	Pattyn[3]	Drenckhan[52]	Bruno[49]
Shortness of breath/dyspnea	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Choking/smothering sensations	x	x	x	x	x		x	x	x	x	x	x	x	x
Fear of dying	x	x	x					x	x	x		x		
Chest pain/discomfort	x	x	x			x		x	x	x				
Tingling/numbness/ paresthesias	x		x			x		x	x	x				
Palpitations/tachycardia		x				x		x	x	x		x		
Dizziness										x				
Flushes/chills				x										
Trembling/shaking						x								
Sweating				x										
Faintness														
Fear of losing control/going crazy											x	x		
Nausea/abdominaldiscomfort				x							x			
Depersonalization/ derealization														

in RS than in NRS patients. However, Panic Disorder Severity Scale (PDSS) scores were similar in both subgroups.[53] Items of specific questionnaires, such as fear of suffocation and fear of other respiratory symptoms, are endorsed more often by patients in the RS than in other PD clusters.[52]

RS exhibited higher agoraphobic and panic-like symptoms and increases in Anxiety Sensitivity Index scores than NRS patients, but there was no subtype distinction based on severity scales (PDSS and Panic and Agoraphobia Scale [PAS]).[35]

Other studies have provided further contradictory data concerning differences in symptom severity and presence of comorbidities between RS and NRS. Beck et al.[59] reported no differences in the number of anxiety and panic signs and symptoms between the two groups; Biber & Alkin[54] likewise found no difference in depression levels. Conversely, Nardi et al.[58] reported that NRS patients experienced more frequent depressive episodes than RS subjects did. Both subtypes had similar scores on anxiety and severity (PAS) scales. In a Portuguese study, patients with the NRS scored worse on the psychological domain of the WHOQOL quality of life questionnaire.[56] Finally, no relationship between suicidal ideation or suicide attempt and the RS has been confirmed.[60]

Several biological markers of PD, such as antioxidant enzymes (glutathione peroxidase and superoxide dismutase), indicators of cellular immunity (adenosine deaminase), biochemical targets (phosphate levels), and genes related to hormone synthesis (namely, the PROGINS variant of the progesterone receptor gene) did not discriminate between RS and NRS.[61-63]

A recent neuroimaging study[64] identified structural differences between the RS and NRS groups, defined according to the criteria of Briggs et al.[29] RS patients had decreased cortical thickness in the frontotemporal cortex, which might be related to perception of respiratory changes (i.e., dyspnea) and emotional deregulation.[64] In another recent study, the magnitude of cardiorespiratory symptoms influenced the activation of some cortical areas (such as the insula) and brainstem in PD patients exposed to panic-related scenes.[65] Taken together, these findings suggest that specific neural regions could be involved in the RS cluster of PD.

In addition to the aforementioned biomarkers, several clinical markers of PD were assessed in a recent review.[66] Structural or functional changes in brain areas, respiratory patterns, and psychophysiological parameters such as heart rate variability could be diagnostic markers of PD. Given the complex and multidimensional nature of the disorder, a combination of different biomarkers and clinical markers (signs and symptoms) could be a reliable strategy to guide better management of PD.[66] Future studies could highlight the utility of simple, low-cost markers, such as heart rate variability and breathing pattern, to discriminate different PD subtypes based on specific symptom clusters.

Respiratory challenge tests

Respiratory challenge tests could constitute reliable tools to distinguish a putative respiratory cluster of PD. Inhalation of elevated CO_2 concentrations is the basis of the most widely studied such test.[31] Exposure to high CO_2 concentrations reliably triggers fear and PA-like respiratory symptoms in humans and animal models.[67] Indeed, CO_2 hypersensitivity may be a risk factor for panic vulnerability.[68]

To test whether patients with the RS are more sensitive to CO_2 inhalation than NRS ones, several studies assessed the prevalence of PA after exposure to a CO_2 challenge test.[25,54,55,69,70] All studies used the Briggs et al. criteria[29] to discriminate RS; however, they were studies were heterogeneous in terms of PA definition and type of CO_2 challenge test

In one study, RS (n=28) and NRS (n=23) subjects were exposed to a single breath of 35% CO_2/65% O_2. A PA was triggered in 79% of RS versus 48% of NRS subjects ($p < 0.05$).[54] Nardi et al.[69] and Valença et al.[55] employed the double-breath 35% CO_2 inhalation test before and after 2 weeks and observed higher PA rates in RS than in NRS individuals in both tests. Freire et al.[25] also found a higher percentage of PA induction in RS than in NRS subjects (80.3% [n=53] vs. 1.8% [n=6], $p < 0.001$) after a single exposure to CO_2. One study found no difference in PA frequency using a distinct CO_2 exposure method (5% CO_2 rebreathing for 5 minutes).[70] However, subjective suffocation, respiratory rate, and voluntary termination of the test were all higher in the RS group.[70] Table 3 summarizes these findings.

Several studies evaluated CO_2 as a potentially sensitive biomarker to identify RS, and found that RS patients are more sensitive to hypercapnia (higher levels of CO_2 in the blood) than those with NRS.[20-22,25] Using similar methodological designs, these studies divided PD patients into CO_2 responders and CO_2 nonresponders, based on the presence (CO_2 responders) or absence (nonresponders) of PA during the double-breath 35% CO_2 inhalation test. RS subtype was defined according to the Briggs et al. criteria.[29] A higher percentage of RS patients was detected among CO_2 responders than among CO_2 nonresponders. Table 4 summarizes the findings of studies assessing the magnitude of CO_2 sensitivity in RS patients.

Response to treatment

Although CO_2 can induce a PA in most patients with PD, pretreatment with a single dose of a benzodiazepine (such as alprazolam or clonazepam) has been shown to block this effect.[71,72] Additionally, treatment with SSRIs and tricyclic antidepressants also reduced the sensitivity to CO_2 in PD patients.[32] RS patients treated with either benzodiazepines or tricyclic antidepressants improved faster than NRS ones. However, in the long run, treatment efficacy was similar in the two groups.[57,58]

RS patients may respond better to tricyclic antidepressants than to benzodiazepines.[30] Moreover, imipramine, alprazolam, nortriptyline, and clonazepam effectively treat all PD patients.[33]

A combination of cognitive-behavioral therapy (CBT) and pharmacotherapy is the first line of treatment for PD. Respiratory exercises emphasizing diaphragmatic breathing are one of the components of CBT, leading to

Table 3 Studies assessing PA rates in RS and NRS subjects after a CO_2 challenge test

Study	RS	NRS	CO_2 challenge test	PA criteria	PA rates in RS, n (%)	PA rates in NRS, n (%)	p-value	Other outcomes
Biber[54]	28	23	Single breath of 35% CO_2 and 65% O_2/breath holding for 5 seconds	Sensation of fear or panic At least four DSM-III-R PA symptoms At least one cognitive symptom	22 (79)	11 (48)	< 0.05	Higher PAS scores and cigarette smoking in RS
Nardi[69]	11	9	Double-breath 35% CO_2 inhalation, breath holding for 8 seconds; test repeated after 2 weeks	Four or more DSM-IV PA symptoms At least one DSM-IV cognitive symptom (fear of dying or fear of going crazy) Sensation of panic or fear resembling real-life PA Agreement of two medical doctors to confirm clinical PA	7 (63.3) (1st test) 9 (81.8) (2nd test)	3 (33.3) 3 (33.3)	0.024 0.011	
Valença[55]	16	11	Double-breath 35% CO_2 inhalation, breath holding for 8 seconds;test repeated after 2 weeks	As in Nardi[69]	15 (93.7) (1st breath) 14 (87.5) (2nd breath)	5 (43.4) 5 (43.4)	0.009 0.033	
Abrams[70]	10	23	5% CO_2 rebreathing challenge for 5 minutes or end-tidal CO_2 pressure > 70 mmHg	At least four DSM-IV PA symptoms At least one cognitive symptom	4 (40)	5 (23)	No statistical difference	Subjective suffocation, respiratory rate, and voluntary termination higher in RS
Freire[25]	66	51	Double-breath 35% CO_2	As in Nardi[69]	53 (80.3)	6 (11.8)	< 0.001	

All studies used the Briggs et al. criteria[29] to define the respiratory subtype of panic disorder.
NRS = non-respiratory subtype; PA = panic attack; PAS = Panic and Agoraphobia Scale; RS = respiratory subtype.

Table 4 Studies assessing CO_2 sensitivity in RS subjects

Study	CO_2 responders, n	CO_2 nonresponders, n	RS among CO_2 responders, n (%)	RS among CO_2 nonresponders, n (%)	p-value
Nardi[20]	62	29	43 (69.3)	12 (41.4)	0.022
Nardi[21]	50	26	31 (62.0)	8 (30.8)	0.011
Nardi[22]	51	32	38 (74.5)	15 (36.9)	0.008
Freire[25]	66	51	31 (47)	4 (5.9)	0.001

CO_2 responders = subjects in whom CO_2 induced a panic attack; RS = respiratory subtype.
All studies used the Briggs et al. criteria[29] to define RS and double-breath 35% CO_2 inhalation as the CO_2 challenge test.

establishment of a regular breathing pattern and reduction of anxiety levels.[73] Thus, considering the presence of common respiratory abnormalities in PD patients, especially in RS, patients in this cluster might derive more benefit from CBT than NRS subjects do. Conversely, some studies have reported no difference between RS and NRS patients under CBT.[63,74]

Breathing techniques focusing on attenuation of hypocapnia (lower levels of CO_2 in blood) and normalization of respiratory pattern seem to help PD patients. Studies measuring end-tidal partial pressure of CO_2 by capnometry during exhalation have found lower levels of CO_2 in RS than in NRS subjects.[59,75] Nevertheless, no studies have assessed the effects of breathing techniques in distinct PD subtypes.

Other interventions which include components that can modulate breathing may be helpful. Yoga involves breath control (pranayamas), meditation, and physical postures. The practice of yoga and a combination of yoga and psychotherapy have been found to reduce anxiety and body sensations in PD subjects.[76] Further investigation of breathing and other physiological parameters could help elucidate the potential mechanisms and efficacy of mind-body practices for management of PD symptoms.

Potential mechanisms underlying the link between panic and breathing

Among the various differences in the clinical presentation of PD across subjects, the respiratory subtype can be well characterized by specific symptoms and tendency toward greater responsiveness to respiratory stimulants (CO_2).

In this context, focus on the RS yields a better understanding of respiratory symptoms and the mechanisms associated with breath control in PD, which considered an important aspect of the pathophysiology of PD and is still poorly understood.

The current evidence base on the pathophysiology of PD includes several hypotheses based on neurobiological, behavioral, and cognitive theories.[2,38,39,77] Alterations in the neural circuitry that involves the brainstem and fear network and impairments in the pH chemosensory system may be the main mechanisms involved in the respiratory abnormalities observed in PD patients.[78-81]

Individuals diagnosed with PD generally have a high perception of danger or threat.[82] To assess a situation as threatening and mount an anxiety-like response, an individual must first detect environmental stimuli through sensory systems and then identify them as aversive or potentially dangerous.[82] The combined actions of distributed neural circuits that emerge from the amygdala, bed nuclei of the stria terminalis, ventral hippocampus, and medial prefrontal cortex result in the interpretation and evaluation of the emotional value of environmental stimuli.[83] If such stimuli are identified as threatening based on this assessment, they may elicit defensive behaviors by recruiting the brainstem and hypothalamic nuclei, resulting in anxious symptoms.[84] The brainstem and its interactions regulate several homeostatic functions, including cardiorespiratory control and chemoreception.[78] PD patients tend to exhibit abnormal brainstem activation in response to emotional stimuli when compared with healthy controls.[65,85]

Acid-base imbalance is another potential mechanism linking breathing and panic.[86] Both CO_2 and lactate, for instance, elicit spontaneous Pas when administered exogenously, as a result of the activation of pH monitoring networks. CO_2 inhalation leads to respiratory acidosis and lactate causes metabolic alkalosis, generating bicarbonate as a byproduct and stimulating CO_2 production. In humans, CO_2 sensitivity lies on a continuum, with PD subjects being highly sensitive to low CO_2 and healthy volunteers only experiencing panic-like symptoms at higher concentrations.[87]

Extracellular pH is a fundamental signal for regulation of homeostatic arousal, with effects on behavior and breathing.[88] Chemoreceptors sensitive to $CO_2/H+$ are activated when pH levels decrease. Among these chemoreceptors, acid-sensitive channels, such as acid-sensitive ion channels (ASICs), transient receptor potential (TRP) channels, the vanilloid receptor 1 (TRPV1), and T-cell death-associated gene 8 (TDAG8), are closely related to the expression of fear. Detection of acidosis triggers ventilatory responses, such as hyperventilation and tachypnea. In patients with PD, elicitation of dyspnea and arousal occur, characterizing the fear sensation. Respiratory and behavioral alterations are the main panicogenic symptoms. In this context, lower pH levels can be considered an interoceptive alarm to trigger a PA.

Inhalation of CO_2 lowers brain pH levels, and this cerebral acidosis activates acid-sensitive circuits (such as ASIC channels) in the amygdala to produce fear and panic.[89] In short, acidosis sensed by acid channels may be translated into the autonomic, behavioral, and respiratory manifestations of a PA.

Conclusion

The respiratory subtype constitutes a distinct cluster of PD, characterized by specific symptoms and a tendency

toward abnormally high CO_2 sensitivity. Studies supported by more specific respiratory symptoms, psychophysiological markers based on cardiorespiratory outcomes, other clinical markers, neuroimaging findings, and respiratory challenges could improve characterization of the respiratory subtype.

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Disclosure

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References

1 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatric Publishing; 2013.
2 Gorman JM, Liebowitz MR, Fyer AJ, Stein J. A neuroanatomical hypothesis for panic disorder. Am J Psychiatry. 1989;146:148-61.
3 Pattyn T, Van Den Eede F, Lamers F, Veltman D, Sabbe BG, Penninx BW. Identifying panic disorder subtypes using factor mixture modeling. Depress Anxiety. 2015;32:509-17.
4 Kircanski K, Craske MG, Epstein AM, Wittchen HU. Subtypes of panic attacks: a critical review of the empirical literature. Depress Anxiety. 2009;26:878-87.
5 Meuret AE, White KS, Ritz T, Roth WT, Hofmann SG, Brown TA. Panic attack symptom dimensions and their relationship to illness characteristics in panic disorder. J Psychiatr Res. 2006;40:520-7.
6 Roberson-Nay R, Kendler KS. Panic disorder and its subtypes: a comprehensive analysis of panic symptom heterogeneity using epidemiological and treatment seeking samples. Psychol Med. 2011; 41:2411-21.
7 Roberson-Nay R, Latendresse SJ, Kendler KS. A latent class approach to the external validation of respiratory and non-respiratory panic subtypes. Psychol Med. 2012;42:461-74.
8 Sinha S, Papp LA, Gorman JM. How study of respiratory physiology aided our understanding of abnormal brain function in panic disorder. J Affect Disord. 2000;61:191-200.
9 Nardi AE, Freire RC, Zin WA. Panic disorder and control of breathing. Respir Physiol Neurobiol. 2009;167:133-43.
10 Kinkead R, Tenorio L, Drolet G, Bretzner F, Gargaglioni L. Respiratory manifestations of panic disorder in animals and humans: a unique opportunity to understand how supramedullary structures regulate breathing. Respir Physiol Neurobiol. 2014;204:3-13.
11 Gorman JM, Fyer MR, Goetz R, Askanazi J, Liebowitz MR, Fyer AJ, et al. Ventilatory physiology of patients with panic disorder. Arch Gen Psychiatry. 1988;45:31-9.
12 Schwartz GE, Goetz RR, Klein DF, Endicott J, Gorman JM. Tidal volume of respiration and ''sighing'' as indicators of breathing irregularities in panic disorder patients. Anxiety. 1996;2:145-8.
13 Abelson JL, Weg JG, Nesse RM, Curtis GC. Persistent respiratory irregularity in patients with panic disorder. Biol. Psychiatry. 2001;49:588-95.
14 Martinez JM, Kent JM, Coplan JD, Browne ST, Papp LA, Sullivan GM, et al. Respiratory variability in panic disorder. Depress Anxiety. 2001;14:232-7.
15 Yeragani VK, Radhakrishna RK, Tancer M, Uhde T. Nonlinear measures of respiration: respiratory irregularity and increased chaos of respiration in patients with panic disorder. Neuropsychobiology. 2002;46:111-20.
16 Grassi M, Caldirola D, Vanni G, Guerriero G, Piccinni M, Valchera A, et al. Baseline respiratory parameters in panic disorder: a meta-analysis. J Affect Disord. 2013;146:158-73.
17 Perna G, Caldirola D, Namia C, Cucchi M, Vanni G, Bellodi L. Language of dyspnea in panic disorder. Depress Anxiety. 2004;20:32-8.
18 Grassi M, Caldirola D, Di Chiaro NV, Riva A, Daccò S, Pompili M, et al. Are respiratory abnormalities specific for panic disorder? A meta-analysis. Neuropsychobiology. 2014;70:52-60.
19 Freire RC, Nardi AE. Panic disorder and the respiratory system: clinical subtype and challenge tests. Braz J Psychiatry. 2012;34 Suppl 1: S32-41.
20 Nardi AE, Valença AM, Lopes FL, Nascimento I, Veras AB, Freire RC, et al. Psychopathological profile of 35% CO2 challenge test-induced panic attacks: a comparison with spontaneous panic attacks. Compr Psychiatry. 2006;47:209-14.
21 Nardi AE, Valença AM, Mezzasalma MA, Lopes FL, Nascimento I, Veras AB, et al. 35% Carbon dioxide and breath-holding challenge tests in panic disorder: a comparison with spontaneous panic attacks. Depress Anxiety. 2006;23:236-44.
22 Nardi AE, Valença AM, Lopes FL, de-Melo-Neto VL, Freire RC, Veras AB, et al. Caffeine and 35% carbon dioxide challenge tests in panic disorder. Hum Psychopharmacol. 2007;22:231-40.
23 Nardi AE, Lopes FL, Valença AM, Freire RC, Veras AB, de-Melo-Neto VL, et al. Caffeine challenge test in panic disorder and depression with panic attacks. Compr Psychiatry. 2007;48:257-63.
24 Nardi AE, Valença AM, Nascimento I, Freire RC, Veras AB, de-Melo-Neto VL, et al. A caffeine challenge test in panic disorder patients, their healthy first-degree relatives, and healthy controls. Depress Anxiety. 2008;25:847-53.
25 Freire RC, Lopes FL, Valença AM, Nascimento I, Veras AB, Mezzasalma MA, et al. Panic disorder respiratory subtype: a comparison between responses to hyperventilation and CO2 challenge tests. Psychiatry Res. 2008;157:307-10.
26 Willgoss TG, Yohannes AM. Anxiety disorders in patients with COPD: a systematic review. Respir Care. 2013;58:858-66.
27 Ciprandi G, Schiavetti I, Rindone E, Ricciardolo FL. The impact of anxiety and depression on outpatients with asthma. Ann Allergy Asthma Immunol. 2015;115:408-14.
28 Holas P, Michałowski J, Gawęda Ł, Domagała-Kulawik J. Agoraphobic avoidance predicts emotional distress and increased physical concerns in chronic obstructive pulmonary disease. Respir Med. 2017;128:7-12.
29 Briggs AC, Stretch DD, Brandon S. Subtyping of panic disorder by symptom profile. Br J Psychiatry. 1993;163:201-9.
30 Freire RC, Perna G, Nardi AE. Panic disorder respiratory subtype: psychopathology, laboratory challenge tests, and response to treatment. Harv Rev Psychiatry. 2010;18:220-9.
31 Amaral JM, Spadaro PT, Pereira VM, Silva AC, Nardi AE. The carbon dioxide challenge test in panic disorder: a systematic review of preclinical and clinical research. Braz J Psychiatry. 2013;35: 318-31.
32 Freire RC, Nardi AE. Panic disorder and the respiratory system: clinical subtype and challenge tests. Braz J Psychiatry. 2012;34 Suppl 1:S32-41.
33 Zugliani MM, Freire RC, Perna G, Crippa JA, Nardi AE. Laboratory, clinical and therapeutic features of respiratory panic disorder subtype. CNS Neurol Disord Drug Targets. 2015;14:627-35.
34 Freire RC, Valença AM, Nascimento I, Lopes FL, Mezzasalma MA, Zin WA, et al. Clinical features of respiratory and nocturnal panic disorder subtypes. Psychiatry Res. 2007;152:287-91.
35 Onur E, Alkin T, Tural U. Panic disorder subtypes: further clinical differences. Depress Anxiety. 2007;24:479-86.
36 Goodwin RD, Hamilton SP, Milne BJ, Pine DS. Generalizability and correlates of clinically derived panic subtypes in the population. Depress Anxiety. 2002;15:69-74.
37 Fullana MA, Vilagut G, Ortega N, Bruffaerts R, de Girolamo G, de Graaf R, et al. Prevalence and correlates of respiratory and non-respiratory panic attacks in the general population. J Affect Disord. 2011;131:330-8.
38 Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. Arch Gen Psychiatry. 1993;50:306-17.
39 Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry. 2000; 157:493-505.
40 Lucki I. The spectrum of behaviors influenced by serotonin. Biol Psychiatry. 1998;44:151-62.
41 Maron E, Shlik J. Serotonin function in panic disorder: important, but why? Neuropsychopharmacology. 2006;31:1-11.

42 Freire RC, Hallak JE, Crippa JA, Nardi AE. New treatment options for panic disorder: clinical trials from 2000 to 2010. Expert Opin Pharmacother. 2011;12:1419-28.
43 Cox BJ, Swinson RP, Endler NS, Norton GR. The symptom structure of panic attacks. Compr Psychiatry. 1994;35:349-53.
44 Bandelow B, Amering M, Benkert O, Marks I, Nardi AE, Osterheider M, et al. Cardio-respiratory and other symptom clusters in panic disorder. Anxiety. 1996;2:99-101.
45 Shioiri T, Someya T, Murashita J, Takahashi S. The symptom structure of panic disorder: a trial using factor and cluster analysis. Acta Psychiatr Scand. 1996;93:80-6.
46 Rees CS, Richards JC, Smith LM. Symptom clusters in panic disorder. Aust J Psychol. 1998;50:19-24.
47 Segui J, Salvador-Carulla L, Garcia L, Canet J, Ortiz M, Farre JM. Semiology and subtyping of panic disorders. Acta Psychiatr Scand. 1998;97:272-7.
48 Neerakal I, Srinivasan K. A factor analytic study of panic symptoms. Indian J Psychiatry. 2002;44:125-30.
49 Bruno A, Muscatello MR, Pandolfo G, Ciura G, Quattrone D, Scimeca G, et al. Does personality matter? Temperament and character dimensions in panic subtypes. Noro Psikiyatr Ars. 2018;55:325-9.
50 Sarp A, Arik AC, Güz H, Sahin AR, Abanoz Z. [Possible subtypes of panic disorder]. Turk Psikiyatri Derg. 2010;21:269-79.
51 Konkan R, Senormanci O, Guclu O, Aydin E, Erkiran M. Evaluating the subtypes of panic disorder by using principal component analysis. J Psychiatry Neurol Sci. 2013;26:333-40.
52 Drenckhan I, Glöckner-Rist A, Rist F, Richter J, Gloster AT, Fehm L, et al. Dimensional structure of bodily panic attack symptoms and their specific connections to panic cognitions, anxiety sensitivity and claustrophobic fears. Psychol Med. 2015;45:1675-85.
53 Song HM, Kim JH, Heo JY, Yu BH. Clinical characteristics of the respiratory subtype in panic disorder patients. Psychiatry Investig. 2014;11:412-8.
54 Biber B, Alkin T. Panic disorder subtypes: differential responses to CO2 challenge. Am J Psychiatry. 1999;156:739-44.
55 Valenca AM, Nardi AE, Nascimento I, Zin WA, Versiani M. Respiratory panic disorder subtype and sensitivity to the carbon dioxide challenge test. Braz J Med Biol Res. 2002;35:783-8.
56 de-Melo-Neto VL, King AL, Valenca AM, da Rocha Freire RC, Nardi AE. Respiratory and non-respiratory panic disorder subtypes: clinical and quality of life comparisons. Rev Port Pneumol. 2009; 15:859-74.
57 Nardi AE, Nascimento I, Valença AM, Lopes FL, Mezzasalma MA, Zin WA, et al. Respiratory panic disorder subtype: acute and long-term response to nortriptyline, a noradrenergic tricyclic antidepressant. Psychiatry Res. 2003;120:283-93.
58 Nardi AE, Valença AM, Nascimento I, Lopes FL, Mezzasalma MA, Freire RC, et al. A three-year follow-up study of patients with the respiratory subtype of panic disorder after treatment with clonazepam. Psychiatry Res. 2005;137:61-70.
59 Beck JG, Shipherd JC, Ohtake P. Do panic symptom profiles influence response to a hypoxic challenge in patients with panic disorder? A preliminary report. Psychosom Med. 2000;62:678-83.
60 Rappaport LM, Moskowitz DS, Galynker I, Yaseen ZS. Panic symptom clusters differentially predict suicide ideation and attempt. Compr Psychiatry. 2014;55:762-9.
61 Pirildar S, Bayraktar E, Berdeli A, Kucuk O, Alkin T, Kose T. Progesterone receptor gene polymorphism in panic disorder: associations with agoraphobia and respiratory subtype of panic disorder. Klinik Psikofarmakol Bülteni. 2010;20:153-9.
62 Ozdemir O, Selvi Y, Ozkol H, Tuluce Y, Besiroglu L, Aydin A. Comparison of superoxide dismutase, glutathione peroxidase and adenosine deaminase activities between respiratory and nocturnal subtypes of patients with panic disorder. Neuropsychobiology. 2012; 66:244-51.
63 Beria P, Viana AC, Behenck A, Heldt E, Manfro GG, Dreher CB. Respiratory subtype of panic disorder: can serum phosphate levels be a possible outcome to group cognitive-behavior therapy? J Affect Disord. 2018;235:474-9.
64 Yoon HK, Kang J, Kwon DY, Ham BJ. Frontoparietal cortical thinning in respiratory-type panic disorder: a preliminary report. Psychiatry Investig. 2016;13:146-51.
65 Feldker K, Heitmann CY, Neumeister P, Brinkmann L, Bruchmann M, Zwitserlood P, et al. Cardiorespiratory concerns shape brain responses during automatic panic-related scene processing in patients with panic disorder. J Psychiatry Neurosci. 2018;43:26-36.
66 Cosci F, Mansueto G. Biological and clinical markers in panic disorder. Psychiatry Investig. 2019;16:27-36.
67 Spiacci A Jr, Vilela-Costa HH, Sant'Ana AB, Fernandes GG, Frias AT, da Silva GS, et al. Panic-like escape response elicited in mice by exposure to CO_2, but not hypoxia. Prog Neuropsychopharmacol Biol Psychiatry. 2018;81:178-86.
68 Roberson-Nay R, Moruzzi S, Ogliari A, Pezzica E, Tambs K, Kendler KS, Battaglia M. Evidence for distinct genetic effects associated with response to 35% CO_2. Depress Anxiety. 2013;30:259-66.
69 Nardi AE, Valença AM, Nascimento I, Zin WA, Versiani M. Carbon dioxide test in respiratory panic disorder subtype. Can J Psychiatry. 2002;47:685-6.
70 Abrams K, Rassovsky Y, Kushner MG. Evidence for respiratory and nonrespiratory subtypes in panic disorder. Depress Anxiety. 2006;23:474-81.
71 Ballenger JC. Efficacy of benzodiazepines in panic disorder and agoraphobia. J Psychiatr Res. 1990;24 Suppl 2:15-25.
72 Nardi AE, Machado S, Almada LF, Paes F, Silva AC, Marques RJ, et al. Clonazepam for the treatment of panic disorder. Curr Drug Targets. 2013;14:353-64.
73 Meuret AE, Wilhelm FH, Ritz T, Roth WT. Feedback of end-tidal pCO2 as a therapeutic approach for panic disorder. J Psychiatr Res. 2008;42:560-8.
74 Taylor S, Woody S, Koch WJ, Mclean PD, Anderson KW. Suffocation false alarms and efficacy of cognitive behavioral therapy for panic disorder. Behav Ther. 1996;27:115-26.
75 Moynihan JE, Gevirtz RN. Respiratory and cognitive subtypes of panic - Preliminary validation of Ley's model. Behav Modif. 2001; 25:555-83.
76 Vorkapic CF, Rangé B. Reducing the symptomatology of panic disorder: the effects of a yoga program alone and in combination with cognitive-behavioral therapy. Front Psychiatry. 2014;5:177.
77 Dresler T, Guhn A, Tupak SV, Ehlis AC, Herrmann MJ, Fallgatter AJ, et al. Revise the revised? New dimensions of the neuroanatomical hypothesis of panic disorder. J Neural Transm (Vienna). 2013; 120:3-29.
78 Perna G, Guerriero G, Brambilla P, Caldirola D. Panic and the brainstem: clues from neuroimaging studies. CNS Neurol Disord Drug Targets. 2014;13:1049-56.
79 Vollmer LL, Strawn JR, Sah R. Acid-base dysregulation and chemosensory mechanisms in panic disorder: a translational update. Transl Psychiatry. 2015;5:e572.
80 Sobanski T, Wagner G. Functional neuroanatomy in panic disorder: status quo of the research. World J Psychiatry. 2017;7:12-33.
81 Quagliato LA, Freire RC, Nardi AE. The role of acid-sensitive ion channels in panic disorder: a systematic review of animal studies and meta-analysis of human studies. Transl Psychiatry. 2018;8:185.
82 Freeston MH, Rhéaume J, Letarte H, Dugas MJ, Ladouceur R. Why do people worry? Pers Individ Dif. 1994;17:791-802.
83 McDonald AJ. Cortical pathways to the mammalian amygdala. Prog Neurobiol. 1998;55:257-332.
84 Adhikari A. Distributed circuits underlying anxiety. Front Behav Neurosci. 2014;8:112.
85 Burkhardt A, Buff C, Brinkmann L, Feldker K, Gathmann B, Hofmann D, et al. Brain activation during disorder-related script-driven imagery in panic disorder: a pilot study. Sci Rep. 2019;9:2415.
86 Friedman SD, Mathis CM, Hayes C, Renshaw P, Dager SR. Brain pH response to hyperventilation in panic disorder: preliminary evidence for altered acid-base regulation. Am J Psychiatry. 2006;163: 710-5.
87 Papp LA, Klein DF, Gorman JM. Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. Am J Psychiatry. 1993;150:1149-57.
88 Magnotta VA, Heo HY, Dlouhy BJ, Dahdaleh NS, Follmer RL, Thedens DR, et al. Detecting activity-evoked pH changes in human brain. Proc Natl Acad Sci U S A. 2012;109:8270-3.
89 Ziemann AE, Allen JE, Dahdaleh NS, Drebot II, Coryell MW, Wunsch AM, et al. The amygdala is a chemosensor that detects carbon dioxide and acidosis to elicit fear behavior. Cell. 2009;139:1012-21.