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Series on Dyspnea. Part 4. A Sensory and Affective Experience of Dyspnea

Series en Disnea. Parte 4. Una experiencia sensorial y afectiva de la disnea

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ABSTRACT

When confronted with a physical stimulus, not everyone feels the same way; each one expresses a sensation with different words; not all of us describe respiratory sensations in the same way; and, why not say it, not all professionals understand what the patient tells them. The psychophysics of dyspnea (quantitative relationships between a respiratory stimulus and a sensation) and descriptors for shortness of breath (the dyspnea language) can help break down communication barriers between patients, family, and health care personnel. General data support a cortical-limbic network for the perception of dyspnea. The insular cortex is widely agreed to be an essential central component of neural circuitry, while the anterior cingulate cortex and dorsolateral prefrontal cortex are thought to modulate the magnitude of dyspnea perception and its relief. Dyspnea has been confirmed in neuroimaging studies as a central nervous system phenomenon, with both sensory and affective dimensions. It has been firmly established that dyspnea is a complex mind-body experience consisting of different sensations that can only be perceived by the individual. The accompanying feelings of distress, fear, and anxiety are driven by affective components, and it is the brain, not the lungs, the one that generates these phenomena.

Key words: Dyspnea; Physiology; Physiopathology; Psychophysics; Descriptors

RESUMEN

No todos sentimos lo mismo ante un estímulo físico, cada uno expresa una sensación con diferentes palabras, no todos describimos de igual forma las sensaciones respiratorias y, por qué no decirlo, no todos los profesionales entienden lo que el paciente les relata. La psicofísica de la disnea (las relaciones cuantitativas entre un estímulo respiratorio y una sensación), los descriptores para referirse a la falta de aire (el lenguaje de la disnea) pueden ayudar a romper las barreras comunicacionales entre pacientes, familia y personal de salud. Los datos generales apoyan una red cortical-límbica para la percepción de la disnea. Hay acuerdo en que la corteza insular es un elemento central esencial para el circuito neuronal, mientras que la corteza cingulada anterior y la corteza prefrontal dorsolateral se cree que modulan la magnitud de la percepción de disnea y su alivio. La disnea como un fenómeno del sistema nervioso central y con dimensiones tanto sensoriales como afectivas, esto ha sido confirmado

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en estudios de neuroimágenes. Se ha establecido firmemente que la disnea es una experiencia compleja de la mente y el cuerpo, que comprende diferentes sensaciones que solo pueden ser percibidas por el individuo. Los componentes afectivos impulsan los sentimientos acompañantes de angustia, miedo y ansiedad, y es el cerebro, no los pulmones, el que genera estos fenómenos.

Palabras clave: Disnea; Fisiología; Fisiopatología; Psicofísica; Descriptores

PSYCHOPHYSICAL LAWS IN GENERAL

No historical account of dyspnea would be complete without mentioning the role of psychophysics. A detailed analysis of this topic is beyond the scope of this article. There are excellent publications by Mahler[1,2] that can be consulted. Psychophysical laws are a set of mathematical expressions that attempt to determine quantitative relationships between the stimulus or input parameters and the sensation or output parameters (perception responses).

The study of non-respiratory sensations dates back to the mid-19th century. The German physician and physicist Hermann von Helmholtz coined the term "psychophysics" and established a precise and non-linear relationship between the magnitude of physical stimuli and the perceived intensity. Helmholtz paved the way for the development of "psychophysical laws". The essential authors of the 19th century are Weber and Fechner, while Stevens and Borg represent the second half of the 20th century and are credited with the application of psychophysical measures to respiratory sensations.

In 1846, Weber reported that the just noticeable difference in intensity between two stimuli is a constant fraction of the intensity of the first stimulus:

$$\text{Just Noticeable Difference} = \frac{\text{delta stimulus}}{\text{Stimulus}} \text{ (it is a constant)}$$

Meaning, the greater the base stimulus (e.g., a sound), the larger the change in stimulus magnitude must be to detect it (this does not hold true for extreme stimuli).[1]

In the late 1950s, Stevens was able to study responses for various sensory modes (light, sound, taste, smell, touch, muscle force, movement).[2-4] He expressed the relationship between the intensity of the stimulus and the magnitude of the sensation with his psychophysical law (or power law):

$$\mathbf{S = c\ E^k}$$

where S is the magnitude of the sensation; c is an arbitrary constant; E is the intensity of the stimulus, and k is the exponent that depends on the sensory modality and environmental conditions. *The exponent k is very relevant as it provides information on how the stimulus is sensorily processed.*

- When k = 1 (visual appreciation of the length of a straight line), the psychological magnitude corresponds directly to changes in the stimulus;
- When it is >1 (electric shock, temperature), small changes in the magnitude of the stimulus expand across a wide range of psychological magnitude,
- and when it is <1 (light, sound), wide ranges of stimulus magnitude are judged as small in terms of psychological magnitude.

PSYCHOPHYSICS OF DYSPNEA

Bakers and Tenney in 1970 were the first to apply Stevens' Law to respiratory variables.[5] In fact, within the respiratory system, the sensory experience is more complex and is studied in terms of relationships between inspiratory pressure and resulting sensation. Not all respiratory stimuli have the same exponent.

The Weber's law would have important implications for the study of patients with abnormal respiratory mechanics, in whom airway resistance and/or lung elastance are often increased. Studies from that time established that:

- Normal subjects over 60 years old perceive less elastic and resistive loads compared to normal subjects under 30 years (they have lower exponent k values).

TABLE 1. Stevens exponent k for respiratory sensations

Type of respiratory load	Exponent k	Comment
Resistive loads (young adults	0.80	What is perceived (S) **is less** than what the stimulus changes (E).
Elastic loads (young adults)	0.95	
Inspired pulmonary volume	1.2	What is perceived (S) **is more** than what the stimulus changes (E).
Static pressures	1.7	

– Patients with COPD (chronic obstructive pulmonary disease) perceive less resistive loads (they have lower exponent k values).
– Normal subjects and asthmatics perceive equally (they have the same exponent k), except in the group with near-fatal asthma (they have lower exponent k values, perceiving less).

Psychophysical laws and the Borg Scale

The result of applying these laws was the conception in 1982 of the well-known Borg Scale and other similar scales.[1-4] The Borg Scale (initially created for the perception of dyspnea during exercise) was able to reconcile an absolute sensory magnitude (0 to 10) with quantitative semantics (mild, moderate, severe, etc.). With some modifications, it is widely used today to quantify dyspnea and muscle discomfort during physical activity. Furthermore, between 1981 and 1989, it was possible to reach two conclusions of interest:[5,6]

– *The intensity of discomfort is proportional to the deviation from the spontaneous ventilatory pattern*. This highlighted the exquisite mechanisms operating to minimize dyspnea in physiological and pathological situations.
– Temporal adaptation, according to which sensory magnitude declines in accordance with a simple exponential function over time (and depending on the magnitude of the respiratory stimulus or load) helped to explain why certain patients can be remarkably asymptomatic with high-intensity stimuli and/or chronic overstimulation.

However, it is worth mentioning that with a better understanding of the multidimensional nature of dyspnea, new precise scales have been developed that evaluate the sensory and affective components of the sensation, and their use should be part of routine care for certain patients.[7]

The language of dyspnea. Descriptors

Our ability to conceptualize and communicate an idea depends on our success in bringing the idea to life through language, and in turn, the physician must be able to decode that language.

When a physician encounters a patient who reports chest pain, they usually ask a series of questions about the intensity and quality of the painful sensation. On a scale from 0-10, what score would you give to your pain? What characteristics does it have? Does it vary with breathing or coughing? Does it radiate to another part of the body? Traditional texts used by medical school students do not discuss the qualitative aspects of dyspnea, perhaps because it is often considered a single sensation.

The concept of dyspnea *quality* has been present since the times of Comroe, Campbell, and Guz, but it wasn't until 1990 that the task of developing a language for dyspnea began, allowing patients and physicians to communicate about inherent respiratory discomfort. In fact, the current definition of dyspnea includes *qualitatively different sensations*.[8]

The attempts to associate certain conditions or diseases with qualitatively specific sensations did not yield the desired results. It is not possible to reasonably assert that a particular type of sensation corresponds to a disease to the extent that it can be diagnostically oriented. There are multiple physiological mechanisms underlying dyspnea in different stages of the disease, as well as multiple sensations that can coexist within a particular patient.

The language of dyspnea is based on how it is communicated, and therefore, the spectrum of descriptors is broad.[9-11] Some of them are used more frequently than others, and while they allow us to understand the distress they generate and the impact produced by that distress (including a sensation of death), they cannot be considered

by any means a clinical guide to direct the causes of dyspnea. Descriptors have been developed by Simon,[9-11] but we do not have a Spanish validation of them.

Attention to the use of verbal descriptors of dyspnea can help the clinician avoid underestimating the severity of airflow limitation when it is not possible to take objective measurements of the lung function. However, there is certain overlap that cannot be ignored, even though the trends appear to be consistent:

- The descriptor *"increased work of breathing"* is associated with COPD, moderate to severe asthma, myopathy, and pulmonary fibrosis.
- Patients with COPD and dynamic hyperinflation sometimes complain of a sensation of *"unsatisfactory/incomplete/short and quick breaths"* or a feeling of *"not being able to take deep breaths."*
- A *"feeling of rapid and shallow breathing"* may correspond to interstitial lung disease or decreased compliance of the chest wall.
- Heart failure is also associated with a sensation of *"suffocation/breathlessness."*
- A sensation of *"heavy breathing"* is typical of deconditioning.

There are multiple communication barriers to understanding the language of dyspnea (Table 2). By developing dyspnea questionnaires, physicians and their patients are more likely to communicate accurately about respiratory symptoms and mechanisms.

It is important to remember that an individual's language, gender, ethnic origin, and culture can influence the wording they use to describe dyspnea.[11]

CENTRAL PROCESSING OF DYSPNEA

Cortical substrate for the perception of dyspnea

By the end of the 20th century, relatively little was known about the ascending pathways responsible for dyspnea. Dyspnea involves several types of receptors and sensations, and it was reasonable to expect that the afferent mechanisms responsible for it were probably more complicated than those for pain. Lines of inquiry aimed at identifying the brain areas for the perception of dyspnea can be grouped into two categories:

- Neurophysiological studies through evoked potential testing.[12-14]
- Imaging studies: positron emission tomography (PET), functional magnetic resonance imaging (fMRI) with blood oxygenation level dependent technique (BOLD).[15-17]

Neurophysiological studies - phrenic afferents

The first study to establish a neurophysiological link between phrenic afferents and the somatosensory cortex was conducted by Frankstein.[12] Until the 1980s, there was a deeply rooted belief that reflexes mediated by afferents in the diaphragm were irrelevant or absent. This conception began to change when it was discovered that approximately 30-45% of the fibers of the phrenic nerve are sensory afferents. It is undeniable that higher centers are interested in the type of activity and the contractile state of the diaphragm. Phrenic afferents contribute to the somatosensation of the diaphragm, conscious perception of breathing, and responses to respiratory load.[18] Figure 1 shows these projections.

TABLE 2. Communication barriers to understanding the language of dyspnea

1) Patients may feel a little unsure about the words they should use, especially if it is their first experience with dyspnea.
2) Physicians' inability to understand the language of dyspnea.
3) Lack of a common vocabulary (language and culture).
4) Traditional notion that all kinds of dyspnea are the same.
5) Dyspnea is less common than pain.

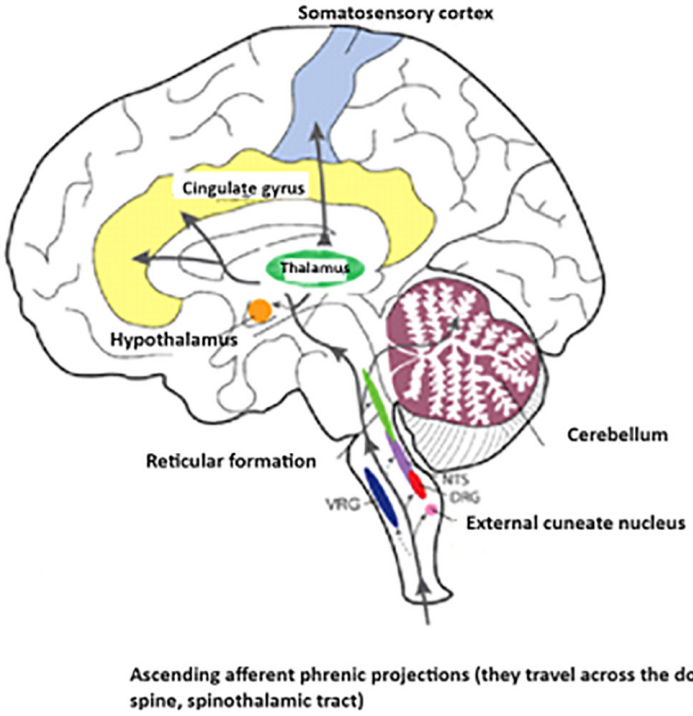

Figure 1. Anatomical projections of phrenic afferent pathways and their functional impact

The phrenic nerve contains fibers from several types of sensory receptors: muscle spindles, tendon organs, ergo- and nociceptors. Sensory outflow from the diaphragm to the spinal cord is somatotopically organized.[19-21] Supraspinal, brainstem, cerebellar, and thalamic projections reach areas with direct and indirect impact on respiratory motor control and modulate the impulse.[21] Supraspinal projections from phrenic afferent neurons have been confirmed in multiple studies, as well as the potential destination of the pathways from diaphragm receptors.[21] VRG, ventral respiratory group; NTS, nucleus tractus solitarius; DRG, dorsal respiratory group.

Phrenic afferents, emotional states, and pain

The fact that phrenic afferents also project to the limbic system in humans suggests a possible link between diaphragmatic sensory afferents and the emotional state: Cortical evoked responses to brief inspiratory occlusions are strongly modulated by affective state in humans. Phrenic afferents may also be involved in shoulder or neck pain. This response likely reflects the activation of group III-IV phrenic afferents that converge with the spinothalamic tract in the high cervical spinal cord.[21]

***In summary**, animal data confirm that diaphragmatic sensory afferents activate neurons in the somatosensory cortex, and human data are entirely consistent with these observations. In addition to modulating respiratory patterns, information transmitted through phrenic afferents contributes to diaphragmatic somatosensation and conscious perception of breathing.*

There is still much to learn about the potential role of phrenic afferents in the activation or modulation of respiratory neuroplasticity, particularly in the context of rehabilitation following neurological injury and/or neuromuscular disease.

Functional imaging studies

While in the early 1990s it was postulated that the rostral projections of respiratory motor neurons from the brainstem to the midbrain and thalamus could represent the central corollary discharge pathway to the sensory cortex,[15] until 1994 the cortical region processing information related to dyspnea remained unidentified.

A PET study on the activation of the respiratory motor command during CO_2 breathing provided the first indication that limbic areas could be involved in the perception of dyspnea.[22] It was pos-

sible to identify neuronal activation in the upper brainstem, midbrain, hypothalamus, thalamus, hippocampus and parahippocampus, fusiform gyrus, cingulate area, insula (considered the fifth cerebral lobe), frontal cortex, temporo-occipital cortex, and parietal cortex. This activation was considered relevant in sensory and motor respiratory responses to hypercapnia in awake individuals.[22,23] Hypercapnia *per se* produces dyspnea, regardless of the increase in ventilation induced by CO_2 (Figure 2).[24]

For equal levels of hyperventilation (HV), during hypercapnia (54.8 mmHg), the sensation of dyspnea was greater than during isocapnia (ISO, 40.2 mmHg). In this group of healthy volunteers, CO_2 induced dyspnea independently of the concomitant increase in ventilation.[24]

Consistent with these findings, Karley et al found that limbic and paralimbic areas activated by CO_2 were located in the anterior insula, operculum, cerebellum, amygdala, thalamus, and basal ganglia. Some frontoparietal elements related to attention were also activated.[25] Respiratory variables represented in these areas included hypercapnia, variations in tidal volume (TV), inspiratory and expiratory resistive loads, and variations in tidal volume under mechanical ventilatory assistance.[16] Brain imaging is unable to distinguish between structures involved in affective and discriminative processing and motor behavioral responses.[26,27]

*In **summary**, studies suggested that the insula is essential for the perception of dyspnea, although current data suggest that the insula acts in concert with a notably extensive and complex neuronal network.*

Sensory and affective components

The pivotal studies from 1995 to 2000 have provided compelling evidence that **sensory intensity** and **unpleasantness of pain** are different dimensions. They even appear to be dependent on separate neural pathways.[28-30] Consistent with these findings, a multidimensional model of dyspnea has been proposed with two components: a) **sensory** (i.e., intensity and quality) and b) **affective** (evaluative, unpleasant).[15,16,30] Davenport and Reep described the two main suggested pathways for processing respiratory sensation in the sensory cortex.[31]

1) It is believed that **sensory aspects (intensity and quality)** predominantly originate in afferents located in the respiratory muscles

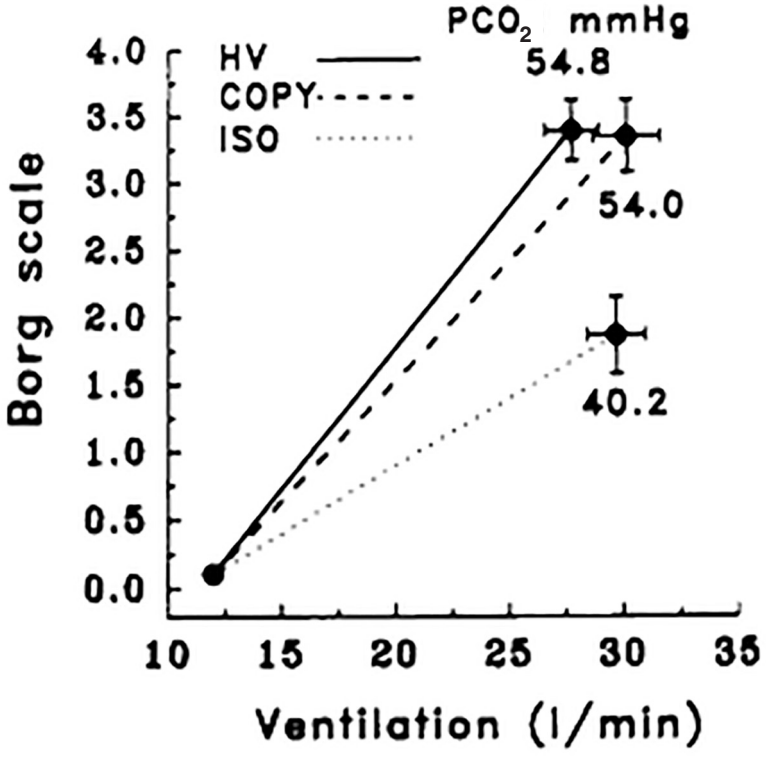

Figure 2. Relationship between the Borg Scale and ventilation to different levels of PCO_2

(phrenic afferents and others), are transmitted to the brainstem, and are projected to the ventral area of the thalamus, from where thalamocortical projections ascend to the primary somatosensory cortex (Brodmann areas 3, 1, and 2) and secondary cortex (Brodmann areas 5 and 7).[16,26,30]

2) **Affective components (evaluative, unpleasant)** appear to go through another pathway. Information, mainly vagal afferents from the lungs and airways, is projected to the brainstem. Brainstem projections ascend to the amygdala and the dorsomedial area of the thalamus and beyond the insula and cingulate cortex. These structures are part of the limbic system, which forms the inner border of the cortex and contains rich interconnections between the cerebral cortex, the thalamus, and the brainstem. The limbic system is also considered important for reward, fear, hunger, thirst, and sexual arousal. The thalamus and hippocampus are believed to be critical neural areas for respiratory sensory input to the cerebral cortex.[16,30]

How does the insula give rise to the perception of dyspnea?

Although there is growing evidence suggesting that the insular cortex acts as a center for interoception and plays a fundamental role in the awareness of subjective feelings rather than simply a role in processing the perception of unpleasantness, it is worth asking how the insula gives rise to the perception of dyspnea.[32]

It has been suggested that increased corollary discharges from the medullary motor command of the brainstem to the respiratory muscles can activate the insula, presumably even *without* peripheral afferent feedback from respiratory mechanoreceptors. Furthermore, although it is unclear whether pain and dyspnea are processed by the same cortical structures or simply by neighboring cortical structures, it is evident that the insular cortex plays an important role in the perception of both sensations.

Lessons from specific clinical situations.

As mentioned, by the end of the first decade of the 21st century, the **multidimensionality** similar to the perception of pain and dyspnea began to be suggested, and includes sensory components (i.e., intensity and quality) and affective components. This approach has clinical implications.[30-32]

1) High sensitivity seems to be favorable because it allows for early detection of deteriorating lung function and rapid relief with medication.
2) A moderate degree of asthma-related anxiety is adaptive because it may be associated with a better perception of bronchoconstriction.
3) On the other hand, the absence of anxiety can lead to indifference and neglect of symptoms.[33]
4) An exaggerated perception of dyspnea, which can lead to excessive use of medical resources, may imply an excessive response in the affective dimension.
5) The affective dimension of dyspnea (displeasure, emotional response) appears not to strictly depend on the intensity of dyspnea.

Davenport et al used respiratory-evoked potential methodology in a group of asthmatic children with a history of near-fatal asthma.[13] They found an absence of an evoked component in 6/11 children after respiratory occlusion (i.e., the sensory signal of dyspnea was not activating the somatosensory cortex). These data suggest the presence of a specific deficit in nearly fatal asthma in the cortical processing of respiratory load information. It is not yet possible to determine whether patients with decreased perception of dyspnea have a specific deficit in the affective rather than the sensory aspects of their perceptual processing.

CONCLUSIONS

A differentiation between the sensory and affective components of dyspnea may be particularly important in improving the accuracy of symptom perception. Neuroimaging studies have shed light on the brain networks involved in the perception of the sensory and affective components of dyspnea. It remains to be determined whether this can contribute to the development of more effective therapeutic strategies for patients with dyspnea.

Neurobiology of dyspnea, endogenous and exogenous opioids

In 1985, Santiago and Edelman postulated that endogenous opioids could be elaborated as a protective mechanism to relieve difficulty breathing.[34] In 2009, O'Donnell proposed a neurobiological model (Figure 3) involving the respiratory and nervous systems that has al-

lowed us to improve our understanding of the perception of dyspnea.[35]

The respiratory system is modulated by excitatory and inhibitory neuropeptides acting from sensory neurons to central networks. Endogenous opioids are inhibitory neuropeptides that affect respiratory rate and nociception. When administering 10 mg of naloxone IV to block opioid receptor signaling, COPD patients reported higher scores of difficulty breathing compared to normal saline administration, both during exercise and with resistive load breathing. These results suggest that endogenous opioids modify dyspnea by acting on the CNS. Opioids modulate dyspnea perception by decreasing the central respiratory drive (and associated corollary discharge), altering the central perception, and/or reducing anxiety.[7,35]

The fear of an overdose and the development of respiratory depression has historically limited the use of opioids to alleviate dyspnea in the clinical practice. However, recent statements from two major global pulmonology societies[27,36] recommend that oral and parenteral opioids be used for the relief of refractory dyspnea. Refractory dyspnea is defined as *"dyspnea that persists at rest or with minimal activity and is distressing despite optimal treatment of advanced lung or heart disease."* In addition to proper titration, communication between physicians, patients, and family members is essential when using opioids for palliative and end-of-life care.[36]

The American Thoracic Society proposed in 2012 that dyspnea be considered in three **constructs**: sensory, affective, and the impact or burden of symptoms. (Table 3).[36] The intensity (sensory) and distress (affective) in response to a specific stimulus have already been discussed. The impact of dyspnea on an individual's daily activities can be considered either during patient care or in a clinical trial. Most of the instruments that are currently being used to quantify dyspnea in clinical trials are relatively recent, dating back to only 30 years approximately (Table 3).

The neurophysiological model provides a conceptual framework to enhance our understanding of the mechanisms contributing to the perception of dyspnea. The opioid system plays a significant role in relieving dyspnea. Both endogenous opioids (β-endorphins) and exogenous opioids (morphine analogs) modulate dyspnea. Interventions that stimulate the release of endogenous opioids require further research to alleviate dyspnea.[7]

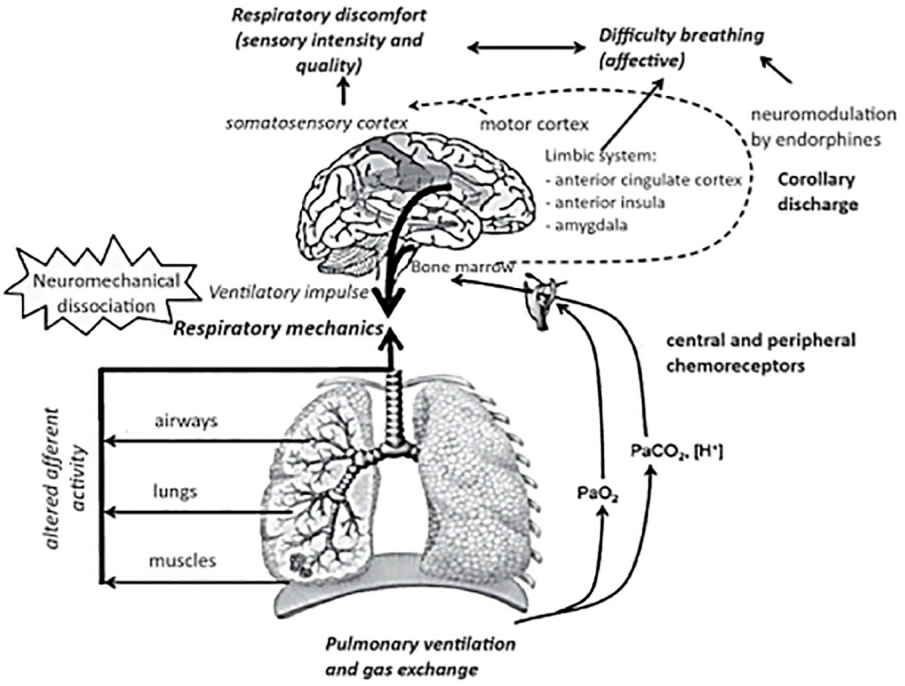

Figure 3. The neurophysiological model provides a conceptual framework to enhance our understanding of the mechanisms contributing to the perception of dyspnea.

TABLE 3. Constructs for dyspnea7: Chronic Respiratory Questionnaire (CRQ); University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ)

Constructos	Descripción	Instrumentos comúnmente utilizados
Intensidad y calidad sensorial	¿Cómo siente su respiración y qué tan grave es?	Escala 0 a 10 Escala análoga visual
Estrés afectivo	¿Qué tan angustiante o desagradable es su respiración?	Escala 0 a 10 Escala análoga visual
Impacto de los síntomas	¿Cómo afecta la respiración a su capacidad funcional?	Escala de disnea del MRC Índice basal y transicional de disnea. Componentes CRQ de disnea UCSD SOBQ

CONCLUSIONS

Comroe's vision on dyspnea as a central nervous system phenomenon, with both sensory and affective dimensions was premonitory and has now been confirmed in neuroimaging studies. Yesterday and today, dyspnea is a primary experience associated with behaviors aimed at counteracting a threat to survival. It has been firmly established that dyspnea is a complex mind-body experience that consists of different sensations that can only be perceived by the individual. Affective components drive the accompanying feelings of distress, fear, and anxiety, and it is the brain, not the lungs, the one that generates these phenomena.[7,36-38]

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