Harnessing the power of anticipation to manage respiratory-related brain suffering and ensuing dyspnoea: insights from the neurobiology of the respiratory nocebo effect

Fabien Vinckier[1,2], Sophie Betka[3], Nathalie Nion[4,5], Laure Serresse[4,6] and Thomas Similowski[4,5]

[1]Université de Paris, Paris, France. [2]Dept of Psychiatry, Service Hospitalo-Universitaire, GHU Paris Psychiatry and Neurosciences, Paris, France. [3]Laboratory of Cognitive Neuroscience, Brain Mind Institute and Center for Neuroprosthetics, Faculty of Life Sciences, Swiss Federal Institute of Technology (EPFL), Geneva, Switzerland. [4]Neurophysiologie Respiratoire Expérimentale et Clinique, INSERM, UMRS1158, Sorbonne Université, Paris, France. [5]Département R3S (Respiration, Réanimation, Réhabilitation respiratoire, Sommeil), AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Paris, France. [6]Equipe mobile de soins palliatifs, AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Paris, France.

Corresponding author: Thomas Similowski (thomas.similowski@upmc.fr)

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The mere expectation of dyspnoea contributes to shape the lives of patients with chronic respiratory diseases: approaches addressing anticipatory mechanisms will provide new therapeutic avenues for persistent dyspnoea in the near future https://bit.ly/3mkv6US

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This issue of the *European Respiratory Journal* presents an elegant study describing the neurobiological basis of a respiratory nocebo effect [1]. The nocebo effect is the dark side of the placebo effect. Both terms designate a gap between an observed effect and what would be predicted on the basis of the known physiological properties of the corresponding intervention. In other words, the placebo effect consists of an unexpected or disproportionate symptomatic improvement relative to what the concerned treatment is expected to produce. For example, saline has no known physiological effect on nociception (the physiological process at the origin of pain) but can have an effect on pain (the symptom resulting from this process). On the contrary, the nocebo effect consists of the worsening or the apparition of symptoms not actually related to the administered treatment. Placebo and nocebo effects are highly contextual [2, 3]. They involve various cognitive mechanisms such as learning or social cognition, and are intimately linked to the notions of belief and anticipation [3]: the placebo component of the effect of a drug strongly depends on what is expected from this drug. Multiple brain systems and neurochemical substances are involved in the underlying neurobiological processes [3], keeping in mind that "there is not one single placebo effect, but many" [4]. Of note, the word "placebo" (and less often "nocebo") tends to be associated with the administration of a treatment. However, non-therapeutic situational stimulation can evoke (or relieve) symptoms depending on prior experience, probably *via* similar anticipatory mechanisms.

Expectation-related phenomena in general have long been described in the respiratory domain. For example, classical conditioning can make an auditory stimulus evoke a hypoxia-like ventilatory response [5]. The placebo effect is also known to be very potent in respiratory medicine [6] and particularly in dyspnoea studies [7–9]. In this context, recent experimental studies have demonstrated that anticipation of dyspnoea activates various brain structures and networks. They include the periaqueductal gray (PAG) [10–13], a brainstem structure located in the midbrain (figure 1) (the activation of which during anticipation directly relates to the intensity of dyspnoea [11]), the anterior insula, the cingulate cortex, and the amygdala [12–18] (key link between respiratory threats, fear and memory [18–21]). Not surprisingly in view of the relationship between dyspnoea and anxiety or fear, a very close relationship exists between dyspnogenic situations (actual or imaginary), previous experience, and anxiety sensitivity [13, 15, 17, 22–25]. Experimental studies have also shown that, like dyspnoea itself [26–28], anticipation of dyspnoea has a negative impact on affective and cognitive brain processes [24, 29]. Finally, experimental and clinical studies have shown

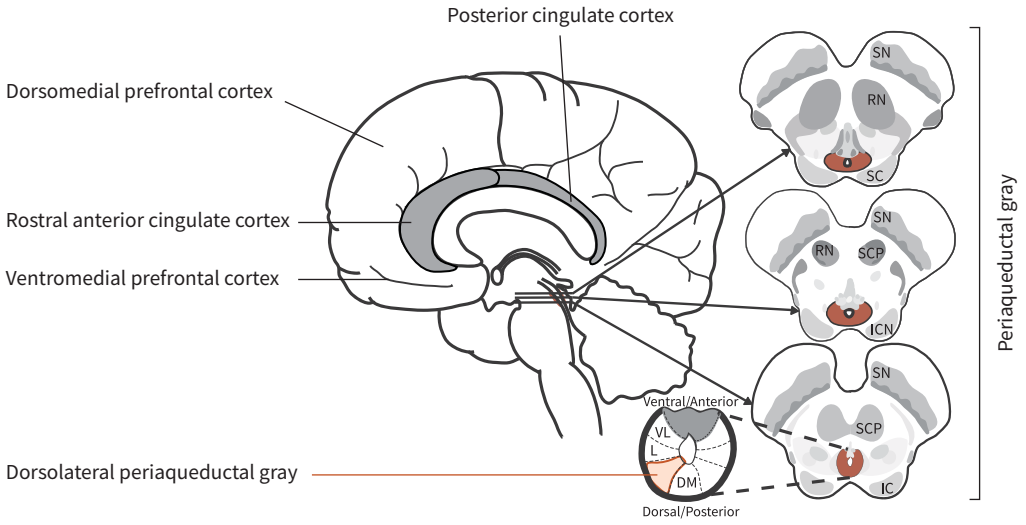

FIGURE 1 Anatomical location of the brain areas involved in the respiratory nocebo effect described by Vlemincx *et al.* [1]. Compared with exposure to the control gas, exposure to histarinol after aversive conditioning resulted in deactivation in the dorsomedial prefrontal cortex, rostral anterior cingulate cortex, and posterior cingulate cortex, and activation in the caudal dorsomedial and dorsolateral periaqueductal gray (PAG; a brainstem structure located in the midbrain that functions as a sensory integrator with strong emphasis on interoception [73] and as an autonomic behavioural control orchestrator [74]; it is involved in the fight, flight or freeze responses to nociception and in the response to perturbations in respiratory-related afferents [74]). SN: substantia nigra; RN: red nucleus; SC: superior colliculus; SCP: superior cerebellar peduncle; ICN: intercollicular nucleus; IC: inferior colliculus; VL: ventrolateral PAG; L: lateral PAG; DM: dorsomedial PAG. Reproduced from [74].

that verbal and visual cues can suffice to induce dyspnoea and the corresponding brain activation [30–33]. Respiratory-related post-traumatic stress manifestations [34–36] also proceed from memory/anticipation mechanisms, and the behavioural sensitivity to respiratory threats (*e.g.* carbon dioxide inhalation) is predictive of post-traumatic stress disorders in animal models [19] and in humans [37].

Respiratory-related expectation is particularly relevant clinically. Although this is not yet fully apprehended by caregivers, expectation shapes the life of patients with chronic respiratory diseases. Attentive clinicians frequently hear remarks like “I do not have to climb stairs to become breathless: looking at them or their mere evocation takes my breath away”. Expectation contributes to determining the nature and intensity of dyspnoea as a symptom, but also to determining its impact as an existential experience. Of note, expectation is by nature governed by intimate factors that are impalpable to others: this is bound to contribute to the “invisibility” of dyspnoea [38–40], an invisibility that impedes access to appropriate care [41] and raises human rights issues [34]. From the above, it ensues that manipulating respiratory anticipation is a logical therapeutic target in dyspnoea. This requires a precise understanding of the corresponding neurophysiological determinants. The study by Vlemincx *et al.* [1] contributes to this knowledge.

What did Vlemincx *et al.* [1] intend to do? They tried to reproduce expectation-induced dyspnoea (a nocebo respiratory effect) in the laboratory by using classical conditioning. They first exposed their subjects to two odoriferous gases: histarinol, which was associated with an inspiratory resistive load (unbeknownst to the participants); and a control gas not associated with loading. This constituted the “experience” phase. They then re-exposed the participants to both gases, but this time with a very mild inspiratory load that was identical for both gases. This constituted the “expectation” phase. To dissect the underlying brain network, the whole experiment was conducted in a magnetic resonance imaging scanner.

What did Vlemincx *et al.* [1] observe? As expected, histarinol was associated with higher dyspnoea scores than the control gas during the “experience” phase. This was also the case during the “expectation” phase, a typical nocebo effect in the absence of any physiologically dyspnogenic stimulus. This psychophysiological phenomenon was associated with activity changes in three types of brain regions (table 1 and figure 1), namely: 1) regions that were activated by the actual inspiratory load, mainly the

TABLE 1 Effects of exposure to histarinol compared to exposure to a control gas

	Experience	Expectation
Conditions	Histarinol plus inspiratory load; control gas plus no load	Histarinol plus small load; control gas plus identical small load
Dyspnoea	Yes (physiological response)	Yes (nocebo effect)
Breathing pattern	No difference	
Brain functional imaging		
Corticolimbic networks		
Insula	Activation	
Dorsomedial prefrontal cortex		Deactivation
Rostral anterior cingulate cortex		Deactivation
Posterior cingulate cortex		Deactivation
Brainstem		
Caudal dorsomedial PAG	Activation	Activation
Dorsolateral PAG		Activation

PAG: periaqueductal gray.

anterior insula; 2) regions that were specifically deactivated when dyspnoea was expected (in contrast to the "experience" phase), mainly the dorsomedial prefrontal cortex and the rostral anterior cingulate cortex (rACC); and 3) regions that were activated by either actual inspiratory loading or dyspnoea expectation, mainly the PAG.

What did Vlemincx *et al*. [1] infer from their results? The pattern of cerebral deactivation observed during the "expectation" phase (rACC and ventromedial prefrontal cortex (figure 1)) constitutes a novel finding regarding the brain response to a respiratory challenge. The authors argue that this response is suggestive of activation of a respiratory nocebo network similar to the pain nocebo network. Indeed, rACC deactivation is observed in nocebo hyperalgesia [42, 43], while, on the contrary, rACC activation is consistently observed in placebo analgesia [44]. Of note, rACC activation is observed during dyspnoea relief [45, 46]. Deactivation of the ventromedial prefrontal cortex, a brain area involved in encoding "value" (*e.g.* economic value of small objects, or, in the field of medicine, value of treatment [42]) is also consistent with a nocebo effect.

As always, there are limitations to the study by Vlemincx *et al*. [1]. The subjects were only exposed to mild inspiratory loading, even in the "experience" condition of the study. The type of dyspnoea induced by inspiratory loading is neither the form most commonly encountered in clinical medicine (where "air hunger" dominates the scene) nor the most aversive (also a prerogative of "air hunger" [47]). The participants were not phenotyped in terms of interoceptive sensitivity or anxiety sensitivity, traits likely to influence the behaviour studied here [15].

What are the implications of the emerging body of data on respiratory expectation? Firstly, from a theoretical point of view, all these data suggest that progress in the understanding of the pathophysiology of dyspnoea and its experiential impact can be achieved by making use of the "Bayesian brain hypothesis". This concept proposes that the brain generates probabilities about the sources of sensory information, exteroceptive (relating to external/environmental stimuli), proprioceptive (relating to stimuli connected to the position and movement of the body) or interoceptive (relating to viscera-arising stimuli) [48]. It also proposes that these predictions are tested against actual incoming information. The mismatch is then used to update/refine the initial hypothesis so that it more accurately predicts sensory input in the future (*via* maximisation of Bayesian model evidence) [49]. Such approaches have been widely applied to perception and action [50, 51] and, more recently, to the understanding of pain perception [52] and of emotional, interoceptive and bodily self-conscious states [53–55]. The prelimbic and limbic cortices (with emphasis on the insula) are thought to play a major role in interoceptive predictions [52, 54] and to do it through dynamic network interactions [54, 55]. Current data concerning the role of the insula in the genesis of air hunger appear to be compatible with the Bayesian brain hypothesis [13, 47]. It is also very likely that the pathogenesis of the various forms of dysfunctional breathing (including the idiopathic hyperventilation

syndrome) involves prediction abnormalities, possibly related to afferent-gating defects. Of note, the "corollary discharge theory", which has been considered central to the pathophysiology of dyspnoea for more than three decades and which postulates that dyspnoea results from an imbalance between the neural drive to breathe and the respiratory afferent traffic to the brain [56, 57], may also be compatible with the Bayesian brain hypothesis.

Secondly, from a therapeutic point of view, the study by Vlemincx *et al*. [1] is important in that it confirms that dyspnoea expectation can be manipulated by an external intervention, making it a relevant therapeutic target. This has already been suggested by data showing that opioids can suppress the conditioned anticipatory dyspnoeic response in healthy subjects [58]. Clinical data have also shown that the respiratory anticipatory brain activity can change during the course of pulmonary rehabilitation, and that this change correlates with reported changes in breathlessness intensity and anxiety [59]. Correction of cognitive distortion and especially erroneous expectations constitutes a cornerstone of cognitive behavioural therapies, which have been shown to be beneficial in patients with chronic respiratory diseases [60, 61]. The emerging effects of medical hypnosis on dyspnoea, which remain to be confirmed [62], could also proceed from similar mechanisms, keeping in mind that interactions between placebo response and hypnotic suggestibility have been described [63] and that hypnotic binding is thought to reflect the Bayesian combination of cross-modal cues [64]. Of major significance, we should keep in mind that the important word in "placebo effect" is "effect". This notion is underpinned by neurophysiological data demonstrating brain responses to the administration of a placebo [65] and by the demonstration that it is possible to boost the placebo effect by manipulating brain excitability [66]. This is also particularly well illustrated by the benefits obtained by open-label placebo ("honest placebo") studies, in which patients who know that they are receiving a placebo still report positive outcomes [67, 68]. As previously advocated [9], this emphasises the importance of gathering data describing the magnitude of the effects of "mere" human interactions on dyspnoea. Experimental data have shown that the presence of others can alleviate experimental dyspnoea [69]; there is therefore little doubt that empathic concern (*i.e.* the "want to help" behavioural consequence of empathy) could be a potent therapeutic tool to help dyspnoeic patients. Many caregivers empirically know that and use it in their daily practice, but specific studies are needed.

Thirdly, from a societal point of view, people witnessing the dyspnoea experienced by others also experience dyspnoea and malaise [33]. With this in mind, the study by Vlemincx *et al*. [1] raises a major question: can vicarious dyspnoea (or dyspnoea by proxy) generate a respiratory nocebo effect in "viewers"? This would be associated with a high risk of empathic distress (*i.e.* the "want to flee" behavioural consequence of empathy) leading to avoidance behaviours that would worsen the invisibility of dyspnoea and further reduce access to care. Here also, specific studies are needed.

In conclusion, we now have substantial evidence showing that the brain is both a culprit and a victim in the "crime of dyspnoea". A victim not only because respiratory suffering impairs brain performance, but also because it fundamentally changes the brain, to the point that, after having been previously exposed to dyspnoea, it becomes capable of generating dyspnoea by itself (typically a vicious circle). This is bad news. But the good news is that the same evidence shows that the underlying neurophysiological mechanisms can be manipulated. This means that to address persistent dyspnoea, the dyspnoea that still bothers patients and makes their lives miserable after all "pathophysiological treatments" have been tried [70, 71] ("treat the lung" [72]), it is of major importance not only to interfere with acute brain mechanisms, including *via* placebo effect-driven interventions ("fool the brain" [72]), but also to reverse chronic conditioning to free the patient's mind from negative respiratory anticipation ("appease the mind" [72]). In this context, the study by Vlemincx *et al*. [1] provides an excellent occasion to stress the importance of harnessing the power of anticipation to optimise the management of dyspnoea.

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