



Review

Breathing control, brain, and bodily self-consciousness: Toward immersive digiceuticals to alleviate respiratory suffering

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ABSTRACT

Breathing is peculiar among autonomic functions through several characteristics. It generates a very rich afferent traffic from an array of structures belonging to the respiratory system to various areas of the brain. It is intimately associated with bodily movements. It bears particular relationships with consciousness as its efferent motor control can be automatic or voluntary. In this review within the scope of "respiratory neurophysiology" or "respiratory neuroscience", we describe the physiological organisation of breathing control. We then review findings linking breathing and bodily self-consciousness through respiratory manipulations using virtual reality (VR). After discussing the currently admitted neurophysiological model for dyspnea, as well as a new Bayesian model applied to breathing control, we propose that visuo-respiratory paradigms -as developed in cognitive neuroscience- will foster insights into some of the basic mechanisms of the human respiratory system and will also lead to the development of immersive VR-based digital health tools (i.e. digiceuticals).

1. Introduction

The increasing number of publications focusing on interoception (i.e. the afferent signaling, central processing, and neural and mental representation of internal bodily signals coming from the viscera and glands; Cameron, 2001; Critchley and Garfinkel, 2017; Betka et al., 2021) testifies of a growing interest in the topic. Such afferent bodily signals have been proposed to inform both affective and cognitive processes; playing an important role in decision making and thus guiding our life choices (Bechara, Tranel, Damasio, & Damasio, 1996; Betka et al., 2017; Gray, Minati, Paoletti, & Critchley, 2010; Kandasamy et al. 2016; Lukowska, Sznajder, and Wierzchoń 2018). Also, a large corpus of research suggests a key role of interoceptive information in the development of selfhood (Craig, 2002; Critchley and Seth, 2012; Park and Blanke, 2019; Schaller et al., 2021; Seth, 2013; Seth, Suzuki, &

Critchley, 2011). Until now cardioception has been most studied, as heartbeats are discrete events and, therefore, easily measurable (Betka, Lukowska Marta, King Joshua, & Hugo, 2021; Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015; Betka et al., 2021). However, several other interoceptive channels exist, including information coming from the respiratory system. Moreover, respiration does not only involve interoceptive signals but also, proprioceptive and motor ones.

Breathing is indeed a very important channel, insofar as it generates an intense afferent traffic from many sources (Adler and Janssens, 2019; Alheid and McCrimmon, 2008; Pal and Chen, 2014). Importantly, many of the respiratory-related afferent messages to the brain are not interoceptive, but proprioceptive: this is a major difference between the respiratory and the cardiac or digestive systems. Each and every breath involves muscles contracting, articulations moving, intrathoracic and abdominal pressure changing, the bronchial tree and lung parenchyma

Abbreviations: rCPGs, respiratory central pattern generators; DRG, dorsal respiratory group; VRG, ventral respiratory group; BSC, bodily self-consciousness; VR, virtual reality.

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being stretched or compressed, air flowing through the upper and lower airway, and cardiac preload and afterload varying. In addition, the overall result of the respiratory activity in terms of gas exchange is integrated by peripheral and central chemoreceptors that are sensitive to changes in blood O₂ and CO₂ (Guyenet et al., 2019; Guyenet, Stornetta, & Bayliss, 2010; Guyenet and Bayliss, 2015). Besides this afferent traffic, and relevant to interoception and bodily self-consciousness, breathing is the only vegetative function that involves an efferent motor control (Butler, Hudson, & Gandevia, 2014). Indeed, breathing depends on a neural control system that is extrinsic to its primary effector - the lungs as the gas exchange apparatus -, namely neural networks located in the central nervous system and driving a complex array of skeletal muscles -the respiratory muscles-. Breathing is itself a movement -variations in rib cage volume involving the contraction of skeletal muscles putting many joints in motion -, but it is also the source of bodily movements -respiratory-related postural oscillations (Johnson et al., 2017; Williams and Carel, 2018).

In this review, we will first describe the general organisation of breathing control. We will then review findings linking breathing and bodily self-consciousness through respiratory manipulations using virtual reality. Then, we will describe the currently admitted neurophysiological model for dyspnea and discuss how predictive coding has been recently proposed to be applied to breathing control and breathing discomfort. Finally, we will discuss clinical implications and possible novel therapeutic applications. We, therefore, place this review within the scope of "respiratory neurophysiology" or "respiratory neurosciences", with the aim to further highlight how the understanding of respiratory-related brain processes and the application of a neuroscientific approach to respiratory medicine is needed to advance the management of dyspnea beyond the correction of its pathophysiological determinants.

2. Breathing control

Among vegetative functions, breathing has several physiological particularities. It is the only vegetative function of which both the very activity and the modulation depends on an extrinsic innervation

-respiratory neural networks located in the central nervous system- rather than on intrinsic nervous automatisms. Indeed, the activity of the heart and the intestines is intrinsically generated (Suchorsky & Rand, 2009). Breathing is the only vegetative function that is mechanically operated by skeletal muscles mobilizing bone joints, leading to movements: breathing generates bodily movements ample enough to require postural compensation (Attali et al. 2019). It is, as a consequence of the two previous characteristics, the only vegetative function for which its automatic control can be superseded by behavioural/voluntary commands that can deeply, if temporarily, compromise homeostatic equilibrium. Also, as a consequence of the above organisation, breathing is the vegetative function that is associated with the most intense and most diverse afferent brain traffic. A summary of the main pathways and neural correlates involved in breathing control is presented in Fig. 1.

2.1. Efferent respiratory pathways: determinants of the neural drive to breathe

The neural drive to breathe is defined as the net outflow of neural commands that reach the respiratory muscle to produce ventilation. It results from the integration and reciprocal interaction of the output of brainstem respiratory central pattern generators (rCPGs) -automatic drive to breathe- and that of respiratory-related cortical networks -behavioural/voluntary drive to breathe-, with respiratory spinal motoneurons playing a crucial role in this integration (Anderson et al., 2016; Baertsch, Liza, Anderson, & Ramirez, 2019; Lane, 2011; Ramirez and Baertsch (2018) and Ramirez and Baertsch (2018)).

2.1.1. Rhythmogenesis and chemosensitivity: brainstem respiratory central pattern generators and modulating neuron groups

2.1.1.1. *Respiratory central pattern generators and their connections.* In mammals, the automatic drive to breathe (rhythmogenesis) is produced in the brainstem (Del Negro, Funk, and Feldman 2018; Ramirez and Baertsch (2018)) by rCPGs that oscillate in response to both pacemaker properties and reciprocal interactions. From an evolutionary point of

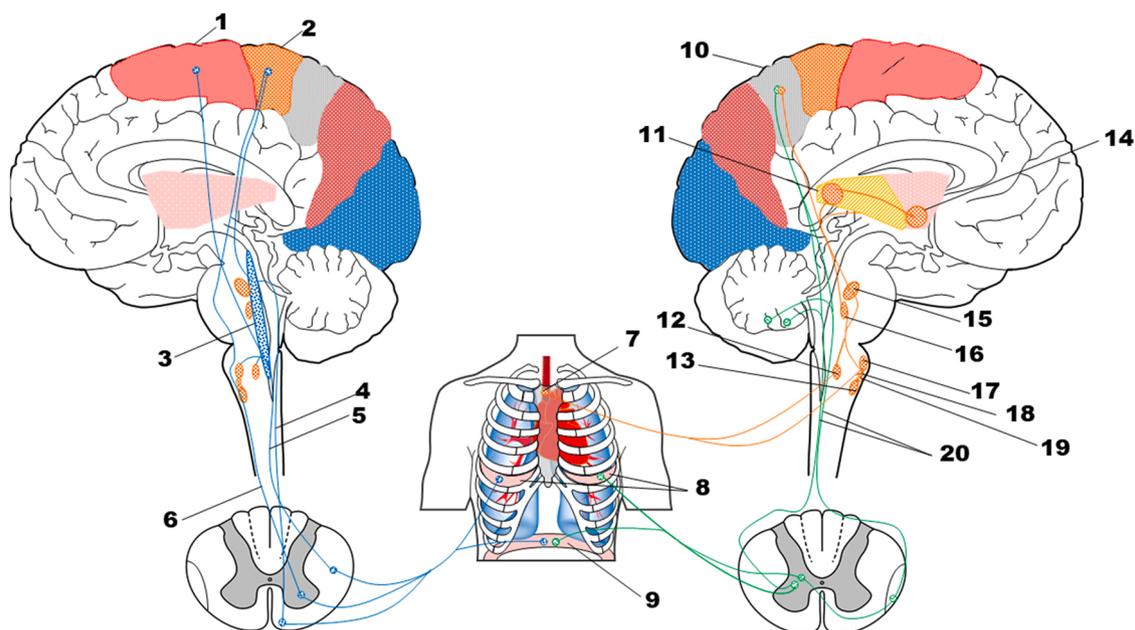


Fig. 1. Schematic representation of the efferent (left) and afferent (right) breathing pathways. 1 = Supplementary motor area; 2 = Motor cortex (M1); 3 = Reticular formation; 4 = medial reticular tract; 5 = Dorsal reticulospinal tract; 6 = Lateral corticospinal tract; 7 = Peripheral chemoreceptors; 8 = Intercostal muscles; 9 = diaphragm; 10 = Primary somatosensory cortex (S1); 11 = Posterior insula; 12 = Dorsal Respiratory Group; 13 = Ventral Respiratory Group; 14 = Anterior insula; 15 = Parabrachial/Kölliker-Fuse complex (Pneumotaxic center); 16 = Apneustic center; 17 = the parafacial respiratory group/retrotrapezoid nucleus; 18 = pre-Bötzing complex; 19 = Bötzing complex; 20 = ventral and dorsal spinocerebellar tracts.

view, this organisation predates air breathing and therefore the evolution of the lungs (Hoffman, Taylor, & Harris, 2016; Perry, Wilson, Straus, Harris, & Remmers, 2001). The dorsal respiratory groups (DRG) and the ventral respiratory groups (VRG) are found in the medulla (Brinkman and Sharma, 2020). DRG respiratory neurons, located in the nucleus tractus solitarius are mostly inspiratory and receive bronchopulmonary vagal afferents (Bolser, Pitts, Davenport, & Morris, 2015). VRG respiratory neurons are both inspiratory and expiratory (Feldman, Loewy, & Speck, 1985). They are located bilaterally in the ventral respiratory column of the medulla, extending from the facial nucleus to the spinal cord (Neubauer, 2006). Their cell bodies lay within the ambiguous and retroambiguus nuclei. The pre-Bötzinger complex, of crucial importance for the rhythmic control of inspiration, belongs to the VRG (Cook-Snyder et al. 2019; Smith, Abdala, Rybak, & Paton, 2009). Recent work suggested that the generation of inspiratory behaviors is underpinned by a wider and spatially dynamic network (Baertsch et al. 2019). While the respiratory network has been described in a series of rostrocaudal compartments (pre-Bötzinger complex, the Böttinger complex and the VRG), it is important to highlight that to date, there is no easily defined anatomical border separating such hypothesized compartments (Baertsch et al., 2019).

Medullary rCPGs receive modulating commands from pontine respiratory neurons that were thought to constitute the apneustic center and the pneumotaxic center (Dutschmann and Dick, 2012) and that are engaged in reciprocal interactions (Zuperku, Krolikowski, Tomlinson, Hopp, & Stuth, 2019). Presumed apneustic neurons project to DRG and VRG respiratory neurons. Their input to DRG respiratory neurons seems to result in prolonged inspiration, due to the delaying of the hypothesized inspiratory off switch signal that is thought to emanate from the pneumotaxic neurons. They are inhibited by vagal afferents and send inhibitory signals to the pneumotaxic neurons. The pneumotaxic neurons are located higher in the pons, within the subparabrachial, medial parabrachial and Kolliker Fuse nuclei. They are not essential to respiratory rhythmogenesis (Simon, 2008) but their input to the rCPGs modulate breathing frequency and tidal volume mostly by regulating the duration of the inspiratory discharge of the rCPGs (Dutschmann and Dick, 2012). More recently, a novel triple oscillator model has been proposed in which the three phases of breathing (i.e., inspiration, postinspiration and active expiration) are generated by three distinct excitatory rhythmogenic microcircuits being the pre-Bötzinger complex, the postinspiratory complex (see Anderson et al., 2016 for further anatomical details) and the lateral parafacial region of the medulla, respectively (Anderson et al., 2016; Ramirez and Baertsch, 2018; Ramirez and Baertsch, 2018).

Pontic respiratory neurons not only project to the medullary rCPGs, but also to the hypothalamus, the NTS and the thalamus (Alheid and McCrimmon, 2008; Fukushi, Yokota, & Okada, 2019). Thalamic neurons have been found to fire synchronously with the efferent respiratory drive, and bursting patterns concurrent with chest and lung expansion have been described (Chen, Eldridge, & Wagner, 1992; Pattinson et al., 2009; Yang and Feldman, 2018). It has been proposed that information conveyed from the chest wall through the medulla and the periaqueductal gray to the thalamus may play a role in conscious -aversive-sensations of breathing and/or to play a role in arousal during sleep (Chen et al., 1992; McGovern, Ajayi, Farrell, & Mazzzone, 2017). The thalamus is believed to be involved in the gating processes that make normal breathing "silent" to the brain (i.e. not reaching consciousness; Chan et al., 2015; Chan et al., 2018) and could therefore possibly play a role in the pathophysiology of dyspnea (see Section 2.3.2).

Finally, projections of brainstem respiratory groups to the cerebral cortex contribute to the genesis of respiratory sensations and are involved in the pathophysiology of dyspnea (see Section 2.3.2; Alheid & McCrimmon, 2008).

2.1.1.2. Chemosensitivity. Beyond the genesis and patterning of the

respiratory rhythm, brainstem respiratory networks are responsible for the adaptation of lung ventilation to the metabolic needs of the body. Some of the brainstem respiratory groups are directly sensitive to changes in cerebrospinal fluid CO₂ content and/or proton concentration (central chemosensitivity; Lumb & Horncastle, 2019). The retrotrapezoid nucleus contains CO₂-sensitive neurons that distribute a CO₂-dependent excitatory drive to rCPGs. Likewise, the retrotrapezoid nucleus' projections to the parafacial respiratory group produce active expiration (Guyenet et al., 2019; Guyenet and Bayliss, 2015; Huckstepp, Cardoza, Henderson, & Feldman, 2015; Zoccal et al. 2018) and projections to the pre-Bötzinger complex increase the inspiratory drive (Del Negro, Gregory, & Jack, 2018; Guyenet et al., 2019). Of importance, CO₂-related activations of the retrotrapezoid nucleus result in increased ventilatory drive and in increased sympathetic activity (Guyenet, 2014). In addition to central chemosensitivity mechanisms, aortic and carotid chemoreceptors monitor arterial blood O₂ and CO₂ and project to brainstem rCPGs via the vagus nerve (peripheral chemoreception; Alheid & McCrimmon, 2008). Of notice, other structures in the brain are known to be CO₂-sensitive, without an apparent direct relationship with homeostasis. Likewise, the amygdala responds to CO₂ changes - via acid-sensing ion channels - in the general frame of threat response (Ziemann et al., 2009). Of importance, in epileptic patients, seizure invasion of the amygdala co-occurred with apnea and O₂ desaturation, and electrical stimulation of the amygdala was able to reproduce these respiratory findings, suggesting a functional connection between the amygdala and brainstem respiratory network in humans (Dlouhy et al., 2015; Rhone et al., 2020).

2.1.2. Cortical and subcortical representations of voluntary breathing control

Other than respiration, there is no other vegetative function that can be controlled outside metabolic needs and neurovegetative inputs. It is impossible to stop one's heart on command, to accelerate intestinal peristalsis voluntarily, or to modulate thermoregulation at will. Yet it is possible to perform voluntary breath holds and to execute relatively complex sequences of respiratory manoeuvres with a limited amount of learning. This ability is put to good use by respiratory physicians to characterize the function of the respiratory system (pulmonary function tests) but can also be used in other contexts (e.g. to control external devices; (Kim and Lee, 2020).

The possibility to perform voluntary respiratory manoeuvres is underpinned by a representation of the respiratory muscles within the primary motor cortex (Colebatch et al. 1991; Foerster, 1936; Gozal et al., 1994; Koritnik, Sheba Azam, Andrew, Nigel Leigh, & Williams, 2009), the direct stimulation of which can generate inspiration or more complex respiratory behaviours (Gandevia and Rothwell, 1987; Maskill, Murphy, Mier, Owen, & Guz, 1991; Penfield and Boldrey, 1937; Sharshar et al., 2004). More recent research is needed to confirm these interesting observations. This representation and the corresponding efferent pathway can be explored in conscious humans through transcranial cortical stimulation (electrical or magnetic; see Gandevia, Butler, Hodges, & Taylor, 2002; Maskill et al., 1991; Similowski, Straus, Coïc, & Derenne, 1996). Neurophysiological data indicate a fast conducting projection, that bypasses the brainstem rCPGs, at least regarding excitatory commands (Corfield, Murphy, & Guz, 1998; Sharshar et al. 2004). A cortical respiratory representation also exists within the supplementary motor cortex, which can be evidenced through targeted transcranial magnetic stimulation (Sharshar et al. 2004), neuroimaging (Colebatch et al., 1991), or electroencephalography (Hudson, Niérat, Raux, & Similowski, 2018; Macefield and Gandevia, 1991; Raux et al. (2007)). It can further be evidenced during voluntary respiratory manoeuvres (continuous —hyperventilation— or discontinuous —sniffing—; Macefield & Gandevia, 1991), in response to various breathing abnormalities, experimental (inspiratory or expiratory mechanical loading; Morawiec, Mathieu Raux, Felix Kindler, Louis Laviolette, & Thomas Similowski, 2015; Raux et al. (2007), hypocapnia-induced silencing of brainstem

rCPGs; Dubois et al., 2016), and during respiratory diseases involving abnormal respiratory mechanics (Launois, Valérie Attali, Mathieu Raux, Isabelle Rivals, & Similowski, 2015; Nguyen et al., 2018), respiratory muscle weakness (Georges et al., 2016) or deficient automatic breathing control (Tremoureaux et al., 2014). Of note, the activation of this premotor-motor respiratory network has been associated with dyspnea (Georges et al., 2016; Morawiec et al., 2015; Raux et al., 2007); see below).

Beyond voluntary respiratory manoeuvres, the respiratory-related cortical network(s) are involved in actions that imply mobilizing the respiratory system for non-respiratory purposes. This has been demonstrated, for example, in the case of speech where a cortical activity specific to the preparation and actuation of prephonatory breaths has been evidenced (Tremoureaux et al., 2014). Similar mechanisms are likely involved in singing and playing wind musical instruments.

However, despite this importance in many functions and medical conditions, respiratory-related network engagement in voluntary breathing control has not yet been fully described. This description is made difficult, when using functional imaging approaches (Colebatch et al., 1991; McKay, Evans, Frackowiak, & Corfield, 2003), by the fact that voluntary manoeuvres imply afferent changes, and the temporary inhibition of automatic breathing commands. This typically occurs during speech, where prephonatory breaths can be actively prepared at the cortical level (Tremoureaux et al., 2014) and where it is necessary to inhibit the rCPGs during the duration of the phonatory expiration (Haouzi, Chenuel, and Barroche 2006). This may explain, for example, why voluntary hyperpnea is associated with neural activity in bilateral primary sensory (S1) cortices (McKay et al., 2003). A role of a fronto-parietal network - also related to planning and attention - has been proposed to underpin the suppression of spontaneous breathing by voluntary breathing command, but the exact mechanisms of such suppression are still unclear (Colebatch et al. 1991; Haouzi et al., 2006; McKay et al., 2003). A bilateral corticobulbar inhibitory pathway involved in voluntary breath holding has also been described in animals and in humans (McKay, Lewis Adams, Frackowiak, & Corfield, 2008; Orem, 1988).

Of importance, the respiratory-related cortical networks do not merely underpin the actuation of respiratory manoeuvres or the use of the respiratory system to non-respiratory tasks. During wakefulness, there is a permanent, "tonic" cortical influence on breathing, as illustrated by respiratory changes in response to repetitive transcranial magnetic stimulation induced neuroplasticity (Laviolette et al., 2013; Nierat, Anna, Chaskalovic, Similowski, & Laviolette, 2015; Raux, Haiqun Xie, Thomas Similowski, & Koski, 2010; Vinit & Pettitjean, 2016; see Section 2.1.3).

Finally, on suprapontine influences on breathing control, it is important to mention that emotion-related respiratory commands originating from the limbic cortex can modify the respiratory neural drive to breathe and result in changes in alveolar ventilation and/or changes in breathing pattern that cannot be explained solely by changes in neurovegetative balance (Boiten, 1998; Heywood et al., 1996). Of note, many areas of the neocortex (e.g., medial prefrontal cortex, hippocampus) show a respiration-locked activity, but the underlying mechanisms and significance of such phenomenon remain to be clarified (Jelincić, Diest, Torta, and Leupoldt (2021); Tort, Maximilian Hammer, Jiaojiao Zhang, Jurij Brankač, & Andreas Draguhn, 2021; Tort, Brankač, & Draguhn, 2018).

2.1.3. Interplay of efferent breathing commands: spinal integration

At any given time, the efferent neural drive to breathe as it can be measured through spirometric, mechanical or electromyographic indicators, results from the integration of brainstem motor commands and of cortical motor commands. This integration mostly takes place at the spinal level and involves motoneuronal facilitation and disfacilitation mechanisms depending on the relative dynamics of bulbospinal inputs (brainstem rCPGs, reticulobulbar tract) and corticospinal inputs

(respiratory-related cortical network, pyramidal tract). The response of a motoneuron to a given descending input depends on its excitatory state, namely the degree of prior membrane depolarization, at the time this input reaches it (Aminoff and Sears, 1971). Likewise, the response to a corticospinal input is faster and greater during tidal inspiration than at the end of expiration (Berger, 1979), being then facilitated by the automatic inspiratory bulbospinal drive (Mehiri et al., 2006). Similarly, CO₂ stimulation increases the output of the rCPGs, which in turn makes responding to a cortical input easier (Straus, Locher, Zelter, Derenne, & Similowski, 2004). This mechanism can be called upon to explain why ventilation decreases more during sleep than would be expected if it just adapted to the reduction of metabolic needs (e.g. sleep-related hypercapnia, possibly in line with spinal disfacilitation in response to the loss of cortical inputs; Mehiri et al., 2006). It has also been invoked to explain the persistence of ventilation during wakefulness in patients with PHOX2B mutations associated with central hypoventilation (Tremoureaux, Raux, Hudson, et al., 2014).

Descending respiratory inputs are not the only contributors to the excitability of spinal respiratory motoneurons. It is also modulated by afferent messages from the respiratory muscles, by somesthetic afferent from the locomotor apparatus (for example, increases in ventilation during sleep in response to ankle mobilisation in patients with defective rCPGs (Gozal and Simakajornboon, 2000) probably relate to this mechanism), or by direct projections from nociceptors. Direct spinal electrostimulation can result in increased ventilation without evidence of change in the activity of rCPGs (Hachmann et al., 2017; Jarosz, Littlepage, Creasey, & McKenna, 2012; Niérat, Similowski, & Lamy, 2014).

2.1.4. From the neural drive to breathe to lung ventilation: respiratory muscles

The neural drive to breathe distributes itself in a temporally and spatially organized manner to upper airway muscles and rib cage/abdominal muscles. This organisation is key to an optimised ventilatory activity, and related abnormalities can translate into serious disorders (e.g. sleep-related apneas; Wilcox, Paré, Road, & Fleetham, 1990). Tonic and phasic contractions of upper airway dilator muscles (e.g., alveolar naris, genioglossus, hypoglossus, glottis, pharyngeal muscles, larynx) do not have a direct effect on lung volumes. They are however crucial in maintaining the patency of the collapsible segment of the upper airway against the alveolo-atmospheric gradients generated by inspiration and expiration, and to minimize airway resistance in conditions of increased ventilatory activity (Brinkman and Sharma, 2020; Cloutier, 2018; Van der Touw et al., 1994; West and Luks, 2016). The main inspiratory muscles are active during resting breathing (e.g. diaphragm, external intercostal, scalene muscles; De Troyer & Boriek, 2011; Sieck, Ferreira, Reid, & Mantilla, 2013). Accessory inspiratory muscles are recruited through augmented bulbospinal inputs in the presence of increased ventilatory demand, e.g., during exercise or in disease. They include the sternomastoid muscles, the serratus anterior, the serratus posterior superior and the latissimus dorsi. All inspiratory muscles increase rib cage volume by lifting the ribs upward. In addition, the diaphragm increases rib cage volume by descending on the abdominal content. Expiratory muscles are generally not active during resting breathing in humans but are recruited as a function of rCPGs activity to meet increases in ventilatory demand. They include abdominal muscles (e.g. external oblique, internal oblique, rectus abdominis and transverse abdominis) as well as the internal intercostals, pectoralis major, and the serratus posterior inferior muscles (Ito, Koji Nonaka, Atsushi Ogi, & Horie, 2016).

The transformation of the neural drive to breathe in alveolar ventilation depends on the intrinsic properties of the respiratory muscles, determining their strength and endurance, on their geometrical configuration, determining their mechanical advantage and their capacity to convert strength into driving pressure. It also depends on the relationship between these characteristics and the impedance of the respiratory system that they have to mobilize. This capacity-load balance, also termed respiratory neuromechanical coupling, is an

important determinant of the pathophysiology of respiratory sensation and dyspnea, within the concept efferent-afferent balance integration (see Section 2.3).

All respiratory muscles can be activated voluntarily to perform respiratory or non-respiratory actions. Interestingly, they also have a role in posture control. Firstly, because they act on the ribs to modify rib cage volume, they mobilize the spine of which the curvature changes during the breathing cycle (Crawford, Dodd, & Engel, 1983; Shirley, Hodges, Eriksson, & Gandevia, 2003). This induces a cyclical, permanent, postural perturbation that must be compensated, e.g. to preserve equilibrium and maintain gaze horizontality. The mechanisms underlying this compensation are central in nature, and they involve cyclical contraction of postural muscles (Attali et al. 2019; Shirley et al. 2003). In addition, the respiratory-related changes in abdominal pressure also involve compensatory mechanisms, with cyclical contractions of pelvic floor muscles (Iscoe, 1998). Secondly, respiratory muscles, as trunk muscles, have a major static and dynamic postural role. They are therefore implicated in a vast array of movements (Gandevia et al. 2002), the actuation of which can interfere with breathing, hence a strong respiratory-locomotor coupling observable in many circumstances (DiMarco, Romaniuk, Von Euler, & Yamamoto, 1983; Lee and Banzett, 1997). Finally, the diaphragm plays a major structural role as a septation organ, separating physically and mechanically the thorax and the abdomen (Perry et al., 2001). This has several positive consequences, including increased lung compliance that varies little with posture and exercise, the optimization of expulsive manoeuvres (with emphasis on parturition (Jones, 1913; Perry, Similowski, Klein, & Codd., 2010), and an inspiratory-related optimization of heart filling through cyclical increases in the abdomino-thoracic gradient (Aliverti et al., 2010; Masmoudi et al., 2017).

2.2. Respiratory-related afferent traffic to the brain

Breath-by-breath respiratory-related afferents relate to many signals including muscle contraction, costovertebral joint movements, changes in intrathoracic and intra-abdominal pressure, changes in bronchial and lung stretching, the flow of air through the upper airway, not forgetting postural information related to respiratory-related oscillations, and respiratory-related changes in cardiac output. The corresponding signals are carried to the brain through several pathways. Proprioceptive information from the respiratory muscles -via stretch sensitive muscle spindles (Nakayama, Niwa, Sasaki, Ichikawa, & Hirai, 1998) and Golgi tendon slowly adapting mechanoreceptors (von Euler and Peretti, 1966)- follow the spinocerebellar tract that is divided in two tracts, a ventral and a dorsal one which arise from the posterior and medial part of the spinal gray matter (Love and Webb, 1992). Afferent information from the upper airway follows a trigeminal pathway to the brain (Mazzone and Udem, 2016).

Afferent information from the lung and bronchi are mostly carried to the brain via the vagal pathway that project to many respiratory-related brain structures, in the brainstem and above (Kubin, Zuperku, & McCrimmon, 2006). Three main categories of receptors have been described in the lung and respiratory tract. A first type of deep, slowly adapting mechanoreceptors, responds to stretch of the airway walls. Such fibres have a large diameter and are myelinated. A second type, rapidly adapting polymodal receptor, has been found in and under the epithelium, sensitive to a panel of chemical (e.g. irritant chemicals such as cigarette smoke) and mechanical stimulations (e.g. lung volume change, congestion). Such vagal fibres have a small diameter and are myelinated. And, finally, a third type of vagal non-myelinated C-fibers functionally is responding to tissue damage; similarly, to nociceptors found in other visceral tissue (Widdicombe, 1982). On top of the information generated by ventilatory movements, integrative chemical afferents inform the brain of the blood content in O₂ and CO₂ (see 2.1.1.2).

2.3. Efferent-afferent respiratory integration

2.3.1. Normal integration: conscious and non-conscious perception of breathing

Respiratory-related afferents project to various areas of the brain. Many of these projections have an important role in regulatory and homeostatic purposes, modulating the activity of the medullary rCPGS and of their pontine controllers (see 2.1.1.1). Other projections are involved in breathing perception, conscious or unconscious.

Respiratory-related projections to the somatosensory cortices (I and SII) are proposed to give rise to the conscious perception of respiratory inputs (e.g., the spatial, temporal and intensity components of the respiratory signals), or respiratory sensations. Respiratory sensation is a term used to denote the conscious perception of breathing without any affective connotation, as opposed to dyspnea which combines the conscious perception of breathing with a negative emotion -predominantly anxiety or fear-; see Section 2.3.2 (Davenport & Vovk, 2009). Of note, -healthy spontaneous- breathing does not normally give rise to any conscious perception. This is postulated to result from respiratory-related projections to the sensory cortex being gated out, most likely at the thalamic level (Chan et al., 2015; Davenport and Vovk, 2009). Physiologically, respiratory ungating can be the result of attentional focus, or of transient changes in the intensity and nature of the respiratory-related afferents, that can themselves result from changes in the efferent regimen (e.g. conscious perception of sighs) (Chan and Davenport, 2009; Herzog et al., 2018; Jelinić, Torta, Van Diest, & von Leupoldt, 2021). In disease, the respiratory gating processes seem to be disrupted in conditions such as generalized anxiety disorder (Chan, Andreas von Leupoldt, Bradley, Lang, & Davenport, 2012;).

There are also direct respiratory-related projections to the limbic cortex, e.g. phrenic nerve mediated afferents to the cingulate cortex (Straus et al., 1997). Limbic structures are involved in the pathogenesis of dyspnea (see Section 2.3.2), probably by playing a key role in allowing respiratory signals to reach consciousness and in linking them to negative emotions. Some evidence also suggests that limbic structures exhibit respiratory-related activity during normal breathing in healthy individuals, namely in the absence of conscious perception of breathing (Farb, Segal, and Anderson 2013). It has been proposed that the posterior insula is a key part of the primary cortical representation of afferent respiratory signals. Likewise, one study has shown that "interoceptive respiratory attention" results in posterior insula activity sensitive to respiratory frequency and increased connectivity between insula and thalamus (Farb, Zindel, & Adam, 2013). This is reminiscent of the postulated representation of cardiac frequency within the insula (). Other studies evidenced respiratory-coordinated neural activity involving the posterior insula during spontaneous, unlabored breathing (Evans, 2010; Evans et al., 2009; Jones et al., 2015). The main limitation of such studies lies in that the authors did not fully correct for respiratory "physiological noise" (i.e., fluctuations of blood-oxygen level dependent contrast of non-neuronal origin): the evidence for respiratory-coordinated neural activity could also be the consequence of stimulus-correlated noise (i.e., movements, vasculature dilation, subsequent changes in cerebral blood flow). In more recent and controlled work, increased activation of the posterior insula was observed if an event -such as loaded breathing- was negatively impacting the homeostatic processes (Harrison et al., 2021). Finally, the posterior insula has been proposed to receive afferent bodily signals while the anterior insula has been proposed to rather project to other cortical and subcortical structures (Gaytán and Pásaro 1998). For example, neurons in the posterior insula are responsive to chemoreceptor stimulations (Hanamori, Kunitake, Kato, & Kannan, 1998) and the anterior insula has been shown to project to brainstem homeostatic centres in the macaque monkey (Saleh, Logothetis, & Evrard, 2017).

2.3.2. Abnormal integration: current conception of the pathophysiology of dyspnea

Dyspnea is a frightening experience that is associated with severe disability and impaired functioning (Parshall et al., 2012). It is defined as an experience of breathing discomfort that can vary in quality and intensity and lead to subsequent physiological and behavioural responses (Parshall et al., 2012). More simply, dyspnea is the conjunction of a conscious perception of breathing activity with negative emotions, most often anxiety and fear. Dyspnea is a medical terminology that several plain language equivalents like breathlessness, shortness of breath, or breathing difficulty. Importantly, respiratory sensations are distinguished from dyspnea.

The exact pathophysiological mechanisms of dyspnea remain to be completely understood. The currently accepted model derives from the corollary discharge principle - also called efferent or efference copy in physiology. Similar to the comparator model (i.e. (Blakemore, Wolpert, & Frith, 2000; Frith, Blakemore, & Wolpert, 2000; Wolpert, Ghahramani, & Jordan, 1995), a copy of the motor respiratory commands produced by the brainstem central respiratory pattern generators and respiratory-related cortical networks (i.e. "the respiratory drive") is thought to be continuously sent to sensory brain areas, in order to simulate "expected" respiratory sensory outcomes (Eldridge and Chen, 1992). Actual afferent respiratory signals are then hypothesized to be integrated and compared to this simulation. Finally, it is postulated that dyspnea arises in the event of an imbalance between the motor drive to breathe, as sensed via the corollary discharge, and the afferent feedback from the respiratory system (Buchanan and Richerson, 2009; Burki and Lee, 2010; Nishino, 2011; Parshall et al., 2012). Inoperant neuro-mechanical coupling, or respiratory muscle load-capacity imbalance (see Section 2.1.4) is, therefore, a major source of dyspnea, mostly of the "excessive inspiratory effort" type (Altose, Cherniack, & Fishman, 1985). A similar imbalance can occur in the impossibility to increase ventilation in response to an increase in CO₂, mostly generating "air hunger" (Banzett, Lansing, and Binks 2021). Interfering with the respiratory corollary discharge could therefore provide a way to mitigate dyspnea independently of any intervention on the underlying respiratory abnormalities.

Implicitly according to its definition (Parshall et al., 2012) and explicitly according to the corollaries that accompany this definition, dyspnea is a symptom, namely something that is verbally described by a patient. There is a long chain of events between the occurrence of a dyspnoegenic physiological abnormality ("stimulus") and what the patient reports ("complaint"). These includes perceptual/sensory processes and cognitive/affective processes, with many possible sources of modulation (e.g. psychological, cultural, or social), making dyspnea a highly multidimensional experience (Lansing, Gracely, and Banzett, 2009). This explains the profound rift that often exists between physiological measures -of lung volumes, of O₂ saturation- and patients' experiences (Carel, 2018). The affective dimension of dyspnea has been related to its association with the activation of limbic cerebral areas. Studies of experimental dyspnea in healthy participants, where breathing discomfort results from the application of mechanical inspiratory loads or from CO₂ stimulation, and studies of clinical dyspnea in patients have shown the involvement of limbic areas such as the anterior and posterior-insula, the cingulate and prefrontal cortices as well as the lateral periaqueductal gray (PAG) (Banzett et al., 2000; Berk et al., 2015; Brannan et al., 2001; Esser et al., 2015; Faull, Jenkinson, Martyn Ezra, & Kyle Ts Pattinson, 2016; Faull and Pattinson, 2017; Herigstad, Anja Hayen, & Kyle, 2011; Herigstad et al., 2017; von Leupoldt et al. 2008; von Leupoldt and Dahme, 2005; Liotti et al. 2001; Raux et al. 2013; Reijnders et al., 2020; Stewart et al., 2014). These areas are key components of the interoceptive network allowing the conscious monitoring of bodily sensations (Craig, 2002; Critchley, 2004). In addition, dyspnea is consistently associated with the activation of a respiratory-related network involving the supplementary motor area, both in experimental and clinical populations (Georges et al., 2016; Morawiec et al.,

2015; Raux et al., 2007). Inversely, relieving dyspnea through mechanical ventilatory assistance is associated with the disappearance of electroencephalographic signs of respiratory-related cortical activation (Georges et al., 2016). The known connectivity between the premotor cortex, limbic areas, and the temporo-parietal junction (Sheets et al., 2020, 2021) makes the respiratory-related activation of this network, also associated with dyspnea (Esser et al. 2015; von Leupoldt and Dahme, 2005), relevant to interoception and bodily self-consciousness (BSC) processes (Park and Blanke, 2019). Of notice, engaging the respiratory-related cortical network in dyspnea-related situations or in breathing activities independent of dyspnea deactivates the default mode network (Raux et al. 2013) that is also associated with self-related processes (Davey, Pujol, & Harrison, 2016). Also, a recent body of evidence indicates that dyspnea can interfere with various cognitive processes and performances (Lawi, Elise Dupuis-Lozeron, Gilles Allali, & Adler, 2020; Nierat et al. 2016; Taytard et al. 2022), through competition for cortical resources, attentional derivation, or both.

Recent work shows that attentional modulation, affective state or - social - context (e.g. experimental social rejection or presence of others) impact dyspnea and its cortical neural processing (Chan et al., 2019; De Peuter et al., 2007; Faull, Hayen, & Pattinson, 2017; Herzog, Sucec, Van Diest, Van den Bergh, & von Leupoldt, 2019; Herzog et al., 2019; von Leupoldt, Corinna Mertz, Sarah Kekat, Swantje Burmester, & Bernhard Dahme, 2006; von Leupoldt, Seemant, Gugleva, & Dahme, 2007; von Leupoldt, Taube, Schubert-Heukeshoven, Magnussen, and Dahme (2007); Nierat et al. 2016; Wilson and Jones, 1990). Moreover, dyspnea can also be induced in patients and healthy participants by paradigms using loaded breathing or the presentation of aversive stimuli (Esser et al., 2017; Faull, Cox, & Pattinson, 2018; Hayen et al. 2017; Juravle, Philipp Reicherts, Mirjam Riechmann-Weinstein, Wieser, & Andreas von Leupoldt, 2017; Nakai et al. 2015; Stoeckel et al., 2015; Stoeckel et al., 2016; Stoeckel, Esser, Matthias Gamer, Christian Büchel, & Andreas von Leupoldt, 2018; Sucec, Michaela Herzog, Ilse Van Diest, Omer Van den Bergh, & Andreas von Leupoldt, 2019; Walter et al., 2020). Dyspnea can even be evoked from verbal or visual cues, in the absence of any actual respiratory change, both in healthy participants (Herzog et al. (2018)) and in patients (Herigstad et al., 2015). Brain responses to anticipatory dyspnea mainly involve the anterior insula, the anterior cingulate, the amygdala, the ventrolateral PAG as well as the motor, parietal opercular and the cerebellar cortices (Faull, Mark Jenkinson, Stuart Clare, & Pattinson, 2015; Faull, Hari, Ezra, & Pattinson, 2019; Faull et al. 2017; Faull and Pattinson, 2017; Hayen et al., 2017;; Vlemincx, Sprenger, & Büchel, 2021). MRI studies at high magnetic field revealed the activation of the ventrolateral PAG during anticipation of loaded breathing and the activation of the lateral PAG during the actual loaded breathing (). Moreover, the lateral PAG was functionally connected to cortical sensorimotor areas during rest and with the amygdala during dyspnea. At rest, the ventrolateral PAG was functionally connected to fronto-limbic areas. However, during dyspnea anticipation, reduced functional connectivity was observed between the ventrolateral PAG and both motor brain areas and lateral PAG (Faull and Pattinson, 2017). These findings led researchers to approach breathing control in general and the pathophysiology of dyspnea in particular in a Bayesian manner accounting for patients' expectations, using the predictive coding framework (Marlow, Faull, Finnegan, & Pattinson, 2019).

2.3.3. Respiratory afferent-efferent integration beyond respiration: breathing and bodily self-consciousness

Recently, the integration of efferent and afferent -including breathing-related - signals from the body have also been proposed to contribute to bodily self-consciousness (Adler, Bruno Herbelin, & Blanke, 2014; Allard, Elisa Canzoneri, Capucine Morélot-Panzini, Bruno Herbelin, & Similowski, 2017; Betka et al., 2020; Monti, Giuseppina Porciello, & Salvatore, 2020), a recent concept of self-consciousness based on low-level perceptual bodily and motor mechanisms (see Section 3).

3. Bodily self-consciousness

3.1. Overview

The experience of interacting with the world as a subject has been proposed to be a low-level self-representation, based on the multisensory integration of bodily signals (Damasio, 1999; Northoff et al., 2006). The study of altered states of self-consciousness in neurological patients (e.g. autoscopic phenomena such as out-of-body experiences) together with experimental manipulations in healthy participants led to the proposition of the general concept of bodily self-consciousness based on multisensory bodily signals and their integration (BSC; Blanke, Mel Slater, & Andrea Serino, 2015; Ehrsson, 2007, 2012; Mohr & Blanke, 2005; Park & Tallon-Baudry, 2014; Tsakiris, 2010). BSC consists of several key conscious experiences. These are (1) *self-identification*, which is the degree to which an individual identifies with the content of his/her global body representation; (2) *body ownership*, which is the feeling that body parts, such as its hands and feet, belong to “me” and are “my” hand or foot; (3) *self-location*, which is the position where one experiences oneself to be, location normally localized within the boundaries of the body, (4) *first-person perspective*, which is the experience of the perspective (position and direction), from where “I” experience to perceive the world; and finally, there is (5) the *sense of agency* which is the feeling of being in control of one’s own actions (Blanke, 2012; Blanke and Metzinger, 2009; Ehrsson, 2012; Tsakiris, 2010). At first, paradigms altering BSC in virtual/mixed reality such as the rubber hand illusion (Botvinick and Cohen, 1998), the full-body illusion or the body swap illusion were focused on the manipulations of exteroceptive (visual or tactile) and proprioceptive stimuli (Lenggenhager, Tej Tadi, & Blanke, 2007; Petkova and Ehrsson, 2008). In such experiments, participants are classically exposed to visual stimulations (e.g., of an avatar projected in front of them through mixed/virtual reality technology, in the case of the full-body illusion, see Fig. 2) and tactile stimulations that are applied either synchronously or asynchronously between their body

and the avatar that they see being stroked. Synchronous vs. asynchronous stimulation interferes with BSC and results in illusory self-identification and self-location toward the virtual body or avatar (Ehrsson, 2007; Guterstam, Malin Björnsdotter, Giovanni Gentile, & Henrik Ehrsson, 2015; Lenggenhager et al. 2007; Maselli and Slater, 2013, 2014; Noel, Christian Pfeiffer, Olaf Blanke, & Serino, 2015; Paluel, Aspell, and Blanke (2011); Petkova et al., 2011; Petkova and Ehrsson, 2008; Pfeiffer, Petr Grivaz, Bruno Herbelin, Andrea Serino, & Olaf Blanke, 2016). Subsequently, these paradigms were extended to include signals coming from within the body, such as cardio-visual instead of visuo-tactile stimulation during the full-body illusion (see below; i.e. (Aspell, Lenggenhager, and Blanke 2009; Capelari, Carlos Uribe, and Brasil-Neto (2009); Crucianelli, Krahe, Jenkinson, & Fotopoulou, 2017; Salomon, Melanie Lim, Christian Pfeiffer, Roger Gassert, & Olaf Blanke, 2013; Suzuki, Garfinkel, Critchley, & Seth, 2013; Tieri, Annamaria Gioia, Michele Scandola, Enea, & Salvatore, 2017).

Visceral interoceptive signalling, for example, the phasic firing of arterial baroreceptors with each heartbeat, has been reported to influence our behaviour (Łukowska, Michał Sznajder, & Michał Wierżchoń, 2018). One can explore the impact of visceral inputs on perception or cognition by time-locking stimulation to certain points of the cardiac cycle. Indeed, within the brain, the magnitude of heartbeat-evoked cortical responses (reflecting the cortical representation of baroreceptor activation), has been found to predict whether or not a visual near-threshold stimulus is successfully detected (Park et al. 2018; Park and Tallon-Baudry, 2014). In some instances, though, visual stimuli are harder to detect if they mirror the phasic timing of the heartbeats (Salomon et al., 2016). Insular activation mediates this effect, showing reduced activation to stimuli presented at the cardiac frequency (Salomon et al., 2016, 2018). In other words, there can be a cancelling out of external stimuli that appear ‘self-related,’ in this case predicted by heartbeat frequency.

Aspell and colleagues adapted the original full-body illusion paradigm to a cardio-visual version by illuminating the virtual avatar

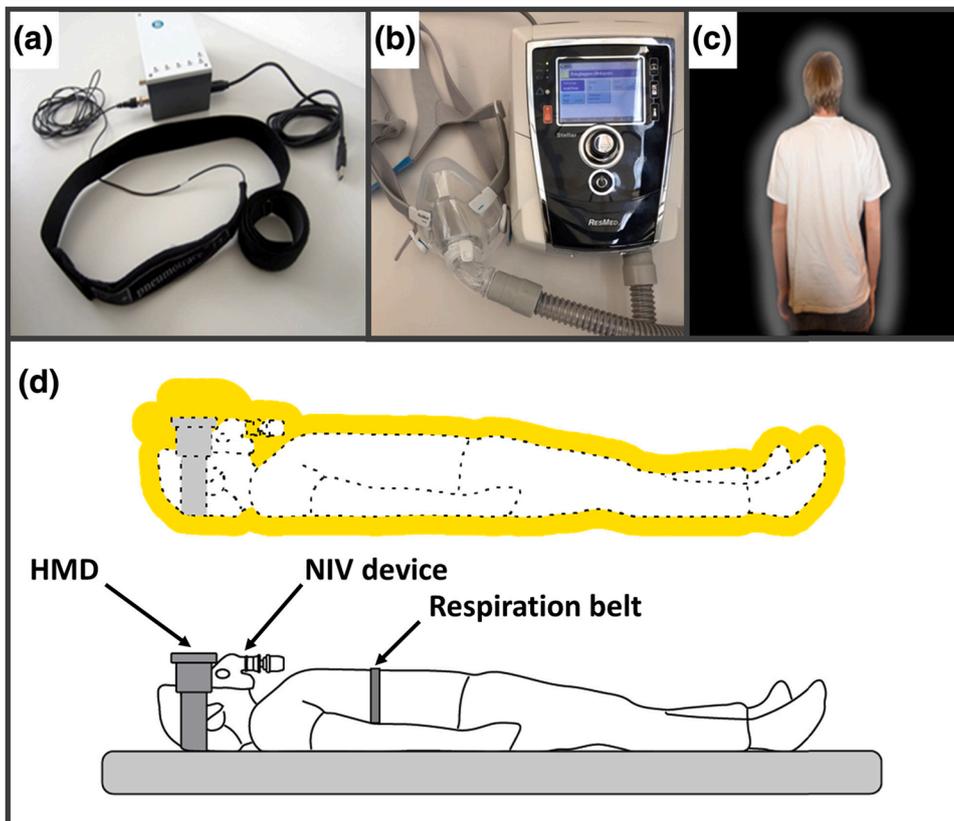


Fig. 2. Example of setup and equipment for the study of respiratory Bodily Self-Consciousness. The subjects are wearing a linear transducer mounted on a respiration belt (a), a non-invasive mechanical ventilation (NIV) device (b). Participants are shown their own back illuminated synchronously (or asynchronously) with respect to their respiratory movements (c). Participants are wearing a Head-Mounted Display (HMD) and were in a supine position (d).

Reproduced from Betka et al., 2020 with permission.

silhouette in synchrony or asynchrony with the participant's heart rate. Participants experienced stronger self-identification, a greater shift in self-location, and changes in crossmodal visuo-tactile integration in the synchronous condition compared to the asynchronous one (Aspell, Bigna Lenggenhager, & Olaf Blanke, 2009). Such cardio-visual changes in self-identification were related to a modulation of the neural activity within the bilateral rolandic opercula and within the parietal somatosensory cortex (Blefari et al., 2017; Heydrich, Jane Elizabeth Aspell, Tom Lavanchy, & Blanke, 2018). These same cardiac signals were reported to enhance illusory hand ownership: in the rubber hand illusion, where individuals are induced to perceive an artificial hand as their own, the effect is strengthened if the artificial hand pulses in synchrony with the participant's heartbeat (Suzuki et al., 2013). Also, transient modulations of neural responses to heartbeats (i.e. heartbeat evoked potentials) in the posterior cingulate cortex and in the insula, covary with changes in bodily self-consciousness induced by the full-body illusion (Park et al., 2016, 2018).

3.2. Respiratory manipulation of BSC

As mentioned, cardioception is often investigated due to the easily extractable nature of the ECG R waves. However, some recent studies also explored the impact of the manipulation of visuo-respiratory signals on BSC.

In this respiratory line of work, Adler and colleagues showed that synchronous flashing of the online recorded respiratory signal onto an avatar silhouette was associated with changes in illusory self-identification and a drift in self-location as well as a greater sense of breathing agency -i.e. the feeling of being in control of the avatar's breathing- towards the avatar. Also, in the synchronous condition, participants became aware of the visual mapping of their respiratory signal, suggesting an "ungating respiratory effect" (e.g. informing the rise of the initially automatic/unconscious breathing signals to consciousness) of such manipulations postulated to be caused by multisensory mechanisms (Adler et al., 2014). In a follow-up study, during mechanically loaded breathing inducing dyspnea, these differences between synchronous and asynchronous conditions in self-location and self-identification were confirmed (Allard et al., 2017). Interestingly, during inspiratory threshold loading induced dyspnea, while no difference between the synchronous and asynchronous conditions was observed for the sense of breathing agency, participants still showed breathing agency toward the virtual avatar but independently from the visuo-respiratory synchronization (Allard et al., 2017). In addition, the affective dimension of dyspnea measured by the Multidimensional Dyspnea Profile (Banzett et al., 2015) was modulated by the visuo-respiratory manipulations: asynchronous stimulations reduced negative emotional state related to breathlessness compared to the other conditions (i.e. synchronous stimulations or absence of stimulations; Allard et al., 2017).

To investigate the contribution of the breathing motor command to the visuo-respiratory full-body illusion and to the sense of breathing agency, we tested participants during active (i.e. participants actively initiate machine-delivered breaths) and passive breathing (i.e. breath cycles are mainly triggered by a ventilator), using non-invasive mechanical ventilation. We replicated all above-mentioned illusory effects but using Bayesian statistics we highlighted an absence of the active vs. passive breathing condition on these changes in bodily self-consciousness. We thus postulated that afferent multisensory signals may be sufficient to induce changes in BSC and may less rely on respiratory-related efferent motor traffic. In addition, participants' breathing pattern was affected by our visuo-respiratory manipulation: increased variability of tidal volume was observed in the asynchronous condition compared to the synchronous condition (Betka et al., 2020). We hypothesized that participants may have unconsciously tried to adapt their respiration to the asynchronous visual flashing ("respiratory mimicry") as previously shown for breathing (Czub and Kowal, 2019)

and other cyclic actions such as walking (Kannape and Blanke, 2013; Menzer et al., 2010).

Recently, several lines of evidence suggest highlighted dependencies between respiration, motor control and the sense of agency (Orset et al., in prep; Park et al., 2020). We thus developed a more systematic investigation of the sensorimotor mechanisms and related motor adaptations underlying breathing agency (Betka et al., in preparation). Finally, when embodied in a 3-D avatar, body ownership and mostly agency -but not perspective- ratings are modulated by the synchrony of the avatar's breathing pattern (compared to an antiphase condition), with accompanying amplitude changes in the participant's breathing (Monti et al., 2020). Such effects were further interacting with participants' interoceptive accuracy, computed using a heartbeat counting task and an auditory pneumoception task. Improved interoceptive accuracy was associated with reduced BSC illusion (Monti et al., 2020). Within a Bayesian framework, this may suggest that precise interoceptive signals and/or better predictions lead to reduced weight given to external cues, and less BSC distortions. Such corpus of studies led researchers to propose a torso-centered BSC system, integrating both interoceptive, somatic and exteroceptive signals from the trunk, informing subjective global unity and temporal continuity (Park and Blanke, 2019). Interestingly, some models suggest that the brain may process bodily signals and physiological function in a Bayesian way (Barrett and Simmons, 2015; Owens, Allen, Ondobaka, & Friston, 2018; Owens, Friston, Low, Mathias, & Critchley, 2018; Samad, Chung, & Shams, 2015).

4. Predictive coding and bodily signals

4.1. Overview

The concept of predictive coding has arisen to understand how the brain makes sense of a continuous barrage of sensory information. It is proposed that the brain is a 'prediction engine' that generates hypotheses about the sources of sensory information then tests these predictions against incoming data. The process generates prediction errors which are used to update the accuracy of the predictive model or to motivate actions/behaviours to resample and/or change the source of the sensory data, a notion called active inference. Predictive coding, error correction and active inference are proposed to be part of a more general Free Energy Principle (Friston, Kilner, & Harrison, 2006). This principle stipulates that the dynamics of any system, which does not dissipate over time, will change of states to maximize Bayesian model evidence (i.e., to maximise evidence of its own existence). In other words, any self-organizing system can be viewed as performing Bayesian inference about the surrounding environment, such that its internal states come to encode probabilistic beliefs about the external environment. The human brain is hypothesised to generate predictions about the world that are based on the learning of stable characteristics of the environment. These predictions inform the interpretation of sensory inputs, by either changing the source of the information by acting on the environment (e.g. moving) or by changing predictions themselves. Predictive coding models are composed of descending (top-down) predictions arising from generative models. In addition, these generative models are constantly updated by ascending (bottom-up) prediction errors. The main goal is to suppress predictions errors, meaning that the predicted signal should be as similar as possible to the received input in order to maximise the predictability of the environment. While this kind of framework has been widely applied to perception and action (Adams, Stewart Shipp, and Friston (2013); Bastos et al., 2012; Hakonen et al., 2017; Hosoya, Baccus, & Meister, 2005; Rao and Ballard, 1999; Shipp, Adams, & Friston, 2013; Spratling, 2008), more recently, predictive coding has been applied to the understanding of emotional, interoceptive and bodily self-conscious states (Ainley, Apps, Fotopoulou, & Tsakiris, 2016; Apps and Tsakiris, 2014; Seth, 2013; Seth and Friston, 2016; Seth et al., 2011). In the context of interoception, it is proposed that affective states are defined through interoceptive predictions of bodily

states. In the Embodied Predictive Interoception Coding (EPIC) model, proposed by Barrett and Simmons, all agranular visceromotor cortices (including cingulate, posterior ventral medial prefrontal, posterior orbitofrontal and ventral anterior insula (AI) cortices) are hypothesized to issue visceromotor predictions which are sent to the hypothalamus, brainstem, and spinal cord nuclei to preserve homeostasis. Agranular cortices are also hypothesized to predict changes in interoceptive signals which will be induced by such homeostatic changes (interoceptive prediction). In response to the afferent signals, primary interoceptive granular cortices (posterior insula) generate interoceptive predictions (errors) back to visceromotor cortices and efferent organs (Barrett and Simmons, 2015). Given its posterior-anterior gradient of dendritic complexity, the insular cortex seems particularly suited to receive interoceptive prediction errors in its mid-posterior part (low integration region), which will be compared to interoceptive predictions generated in the more anterior part (high integration region) (Anderson et al., 2009; Galloway, Jeanmonod, Rouiller, & Morel, 2012). Some recent evidence supports the implication of the anterior insula in the representation and updating of models of bodily states (Harrison, Nanz, et al., 2021). For example, air hunger, a conscious sensation of unsatisfied breathing that is strongly associated with fear, is a key component of dyspnea (see above). It mostly arises as a threat response to compromised homeostasis (e.g. hypercapnia). Yet air hunger has been associated with activation of the anterior part of the insular cortex (Banzett et al., 2000; Banzett, Robert, & Andrew, 2021; Brannan et al., 2001; von Leupoldt et al., 2008; Liotti et al., 2001). However, it is important to note that the anterior insula is activated by a large number of different stimuli, including non-aversive stimulations (Harrison, Hayen, Wager, & Pattinson, 2021) and may rather reflect the precision of priors rather than the strength as well as the intensity of dyspnea (Finnegan et al., 2021; Harrison et al., 2021).

4.2. A Bayesian approach of breathing control and of the pathophysiology of dyspnea?

The Bayesian framework has been tentatively applied to dyspnea, in order to explain the gap between the conscious dyspnea experience and the observed physiological measures (Carel, 2018; Faull et al., 2019; Faull, Marlow, Finnegan, & Pattinson, 2018; Hayen et al., 2017; Marlow et al., 2019). Some recent evidence suggests that the ventrolateral PAG may be an important hub of the integrated brain respiratory network. Given its specific pattern of anticipatory activations and its structural connectivity with other visceromotor areas, the PAG is hypothesized to receive bodily state predictions from the agranular cortices and to encode prediction errors (i.e. mismatch between the expected and the actual sensory inputs). Neuroimaging evidence supporting a relationship between PAG and interoceptive predictions errors were found (Harrison et al., 2021). Affective states and traits -such as anxiety- may modulate expectations/predictions regarding dyspnea and then bias the perception of breathing signals leading to what is at times (and erroneously) termed "disproportionate dyspnea" (; Marlow et al., 2019). For example, a shift in the anterior insula processing of threat valence induced by the prediction of breathing resistance has been shown in anxious participants (Harrison et al., 2021). Expectations/predictions may also be modulated by past experiences; the amygdala is chemosensitive to CO₂ and may play a key role in such memory-related source of modulation (Ziemann et al., 2009). However, the exact mechanism(s) underlying dyspnea within such Bayesian framework (e.g. biased prediction toward dyspnea sensations? Imprecise sensory signal? Both?) remain to be clarified. Nevertheless, the use of predictive models to explain breathing control and the pathophysiology of dyspnea is opening new avenues for research, interpretation and potential interventions; focusing on the anticipatory response rather than on the respiratory outcome.

5. Applications to the clinical management of dyspnea and future perspectives

The starting point of treating dyspnea always involves correcting the respiratory, cardiac, or neuromuscular abnormalities of which dyspnea is the symptom (i.e. "treat the lungs"). When these abnormalities cannot be corrected because they are not reversible — persistent dyspnea —, or, in the cases of dysfunctional breathing and idiopathic hyperventilation, when there is no physiological abnormality to correct, the brain becomes the only possible target of dyspnea-relieving interventions. A large array of such brain-targeted respiratory interventions has been proposed (see Similowski, 2018), some of which are readily used in clinical practice while others are still at the research stage. Some of these interventions aim to directly modify brain respiratory responses. These include the administration of opioids (Abdallah et al., 2019; Hayen et al., 2017), known to alleviate dyspnea irrespective of their effects on the neural drive to breathe, or the induction of neuroplasticity through repetitive transcranial magnetic stimulation (Nierat et al., 2015). Despite studies showing effects in acute administration, recent evidence from clinical trials have challenged the benefit of oxycodone or morphine over placebo for the treatment of persistent dyspnea (Currow et al., 2020; Ferreira et al., 2020). Other data suggest that in severe COPD chronically administered opioids may taper off dyspnea peaks and improve disease-specific health status (Verberkt et al., 2020). Other interventions aimed at "fooling the brain", by strengthening the respiratory-related afferent traffic independently of actual respiratory changes. This is the case of furosemide inhalation to stimulate bronchial stretch receptors (Grogono, Clare Butler, Hooshang Izadi, & Moosavi, 2018) or of menthol inhalation and of the projection of airflow to the face to stimulate trigeminal receptors (Kanezaki and Ebihara, 2017; Nishino, Tagaito, & Sakurai, 1997). Finally, other relevant brain-targeted dyspnea interventions rely on modifying dyspnea-related affective and cognitive processes. In this domain, mindfulness, hypnosis, and cognitive behavioural therapies have been proposed (Anlló, Bertrand Herer, Yolaine Bocahu, Valérie Mach Alingrin, & Larue, 2020; Tan et al., 2019).

We believe that virtual reality (VR) could prove a very fruitful way to address the management of persistent dyspnea. Indeed, VR has been beneficial for fundamental research but also for the development of potential new immersive digiceuticals. The term digiceutical is also known as a digital therapeutic or a digital health tool. VR is a unique technique that allows precise control of the experimental environment, increasing possibilities for replication (Bohil, Alicea, & Biocca, 2011). Using this approach, researchers can modulate variables that cannot be modulated in real life (e.g. appearance of the body) and have increased interactivity between the participant and the virtual environment (Tajadura-Jiménez, Domna Banakou, Nadia Bianchi-Berthouze, & Slater, 2017). Following studies in healthy participants on BSC, experimental paradigms using VR have been developed and applied to clinical populations (Pozeg et al., 2017; Rognini et al., 2019; Solcà et al., 2020; Solcà et al., 2018). For example, synchronous multisensory visuo-tactile neural stimulation induced higher prosthesis embodiment and reduced the distorted perception of a phantom limb in amputated patients (Rognini et al., 2019). Recently, VR based immersive digiceuticals became popular in the field of pain management (Donegan, Ryan, Swidrak, & Sanchez-Vives, 2020; Matamala-Gomez et al., 2019; Trost, Christopher France, & Shum, 2021). In one such study, the synchronous flashing of cardiac signals on a virtual limb has been shown to reduce pain ratings, increase muscle strength of the affected limb, and modulations of physiological pain correlates (e.g. heart rate variability) in patients suffering from complex regional pain syndrome and thus without applying any stimulus to the affected limb (Solcà et al., 2018).

In the respiratory domain, it has already been shown that asynchronous visuo-respiratory stimulations during the full-body illusion were associated with reduced negative emotional state related to breathlessness (Allard et al., 2017), changes in tidal volume variability

(Betka et al., 2020) and changes in respiration amplitude (Monti et al., 2020). Based on these visuo-respiratory findings in human neuroscience and the already established clinical impact on chronic pain using BSC manipulations mediated via VR (Rognini et al., 2019; Solcà et al., 2018, 2020), we propose that the described visuo-respiratory paradigms or future adaptations may also be of relevance as immersive digiceutical therapies for patients suffering from a range of respiratory disorders. Based on these findings, we recently investigated the clinical impact of an adapted visuo-respiratory paradigm using a VR compatible smartphone, and its feasibility, in patients suffering from persistent dyspnea (due to COVID-19 infection), in a clinical setting (Betka et al., 2021). We found that during synchronous visuo-respiratory stimulation, breathing comfort significantly improved compared to control and baseline conditions. A similar effect of the intervention was observed for breathing agency -i.e., the feeling of being in control of one's breathing. Finally, the vast majority of the sample reported global satisfaction regarding the VR intervention and, more importantly, indicated that the immersive VR feedback improved their breathing (Betka et al., 2021). Future randomized clinical trials should investigate whether such VR-based interventions, especially if repeated over time have long-lasting effects, whether such VR-based interventions are possible treatments patients could carry out at their homes, and whether different respiratory pathologies associated with dyspnea (such as chronic obstructive pulmonary disease (COPD) or hyperventilation syndrome) can benefit from immersive digiceutical treatments. We note, however, that more basic neuroscience research is still necessary to improve diagnostic and therapeutic stimulations using VR and manipulations of bodily self-consciousness related to respiration. Better measurements to quantify dyspnea and BSC variables are needed. Also, the neural mechanisms underlying such visuo-respiratory effect using immersive digiceuticals in healthy participants as well as different patient populations need to be determined.

This being said, we believe that improved data analysis including Bayesian approaches will also be important to better understand and potentially treat dyspnea (Harrison et al., 2021). May our VR visuo-respiratory manipulations improve predictions or the precision of the sensory signal leading to reduced negative breathlessness-related affects? For example, one could expect that providing synchronous visuo-respiratory feedback may improve the precision of respiratory sensory signals which would then increase the influence of sensation on perception and reduce the impact of inaccurate -affective- predictions in patients suffering from breathlessness (Harrison et al., 2021; Marlow et al., 2019). Would then the visuo-respiratory manipulations during loaded breathing be underpinned by reduced functional connectivity between the lateral PAG and limbic areas such as the anterior insula or amygdala (see Faull and Pattinson, 2017; Harrison et al., 2021) and how do they depend on the neural systems described for bodily self-consciousness (i.e.; Park and Blanke, 2019) and agency networks (Nahab et al., 2011; Nahab, Kundu, Maurer, Shen & Hallett, Nahab, Kundu, Maurer, Shen & Hallett; Nahab, Kundu, Maurer, Shen, & Hallett, 2017). Such exploration will be rendered possible by the novel possibility to use immersive VR inside an fMRI scanner (Gauthier, Albert, Martuzzi, Blanke, & Herbelin, 2021; Moon, Baptiste Gauthier, Hyeong-Dong Park, Nathan Faivre, & Olaf Blanke, 2020). Could we, by exposing patients suffering from persistent dyspnea to VR visuo-respiratory manipulations during several sessions, reduce symptoms and potentially improve pneumoception? For example, Garfinkel and colleagues developed an anti-anxiety therapy based on the realignment of interoceptive dimensions using cardio-auditory stimulations (Garfinkel, McInachan, & Critchley, 2017). Another interesting point for future research would be the extension of our visuo-respiratory paradigm to the auditory -or other sensory- domains. Both healthy and pathological breathing patterns are usually producing prominent auditory cues, which are both informative in terms of homeostasis and clinically relevant (Faiezpour and Abuzneid, 2020; Monti et al., 2020; Pellegrini and Ciceri, 2012). If dyspnea-alleviating immersive

digiceutical applications are tapping into multisensory integration, we would expect that such therapies should also be efficient in different sensory modalities.

6. Conclusions

Breathing control is a complex process that depends on different highly integrated pathways underpinning both automatic and voluntary commands. Breathing control involves brain's motor, sensory and limbic areas as well as midbrain structures, underlying the multidimensional aspects of such system. The use of advanced Bayesian modelling approaches in respiratory medicine and its combination with VR are promising and open new directions towards a better understanding of the physiology of breathing and of the pathophysiology of dyspnea. Finally, respiratory-related signals play a crucial role in the torso-centered bodily self-consciousness system. Moreover, even though the potential mechanisms should be further investigated, and integrated into a Bayesian model of breathing control, we already showed that visuo-respiratory manipulations alleviate negative affects during dyspnea. Such findings have important clinical implications and could inform the development of virtual reality-based immersive digiceuticals as neuro-respiratory therapeutic tools.

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