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The Integrative Role of the Sigh in Psychology, Physiology, Pathology, and Neurobiology

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Abstract

"Sighs, tears, grief, distress" expresses Johann Sebastian Bach in a musical example for the relationship between sighs and deep emotions. This review explores the neurobiological basis of the sigh and its relationship with psychology, physiology, and pathology. Sighs monitor changes in brain states, induce arousal, and reset breathing variability. These behavioral roles homeostatically regulate breathing stability under physiological and pathological conditions. Sighs evoked in hypoxia evoke arousal and thereby become critical for survival. Hypoarousal and failure to sigh have been associated with sudden infant death syndrome. Increased breathing irregularity may provoke excessive sighing and hyperarousal, a behavioral sequence that may play a role in panic disorders. Essential for generating sighs and breathing is the pre-Bötzinger complex. Modulatory and synaptic interactions within this local network and between networks located in the brainstem, cerebellum, cortex, hypothalamus, amygdala, and the periaqueductal gray may govern the relationships between physiology, psychology, and pathology. Unraveling these circuits will lead to a better understanding of how we balance emotions and how emotions become pathological.

Keywords

anxiety; panic; arousal; cardiorespiratory; PAG; rhythm generation; SIDS; breathing; pre-Bötzinger complex

1 INTRODUCTION

Breathing is an essential component of life, and must be maintained from the first to the last breath. Disturbances in the neuronal control of breathing have devastating consequences and may ultimately be fatal. Various neurological conditions are associated with severe breathing disturbances. These disorders include multiple system atrophy (Schwarzacher et al., 2011), Rett syndrome (Ramirez et al., 2013b; Weese-Mayer et al., 2006, 2008b), Familial Dysautonomia (Carroll et al., 2012; Weese-Mayer et al., 2008a), sudden infant death syndrome (Garcia et al., 2013; Kinney et al., 2009; Paterson, 2013), congenital central

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hypoventilation syndrome (Ramanantsoa and Gallego, 2013), sleep apnea (Gozal and Kheirandish-Gozal, 2008; Ramirez et al., 2013a), Pitt Hopkins Syndrome (Gallego, 2012), and sudden death of epilepsy (Kalume, 2013; Sowers et al., 2013). Thus, understanding how breathing is generated within the nervous system and how the CNS controls ventilatory functions is of great clinical interest.

But breathing does not have an important role only in controlling ventilatory functions. This behavior has been implicated in the control of a variety of central nervous system functions that are not obviously associated with the control of lung ventilation. Indeed, breathing is perhaps one of the most centrally integrated motor behaviors with functional roles that reach well beyond a "simple control of lung ventilation." Most respiratory physiologists are aware of the fact that respiratory activity changes dramatically during wakefulness and sleep, and that modulatory and sensory control of breathing is state dependent. But, surprisingly, many scientists have no appreciation, or only very little knowledge, that breathing also has "nonventilatory" functions. Breathing behavior is, for example, highly influenced by emotional states. This behavior is greatly affected by negative (panic, anxiety, and pain) and positive emotions (pleasure, love, and relief), and one of the purposes of this review is to discuss the possibility that breathing is modulated by various circadian, cognitive, and emotional brain states, and at the same time itself plays a major role in centrally affecting emotions, arousal, and other brain states. Breathing disturbances, such as hyperventilation and an increased sigh frequency, are characteristic of panic disorders. And we will argue that hyperventilation is possibly causal for the initiation of panic. Hyperventilation-induced seizures are another example of a brain state that may be centrally caused by the respiratory system (Tsiptsios et al., 2010; Yang et al., 2011). Although hyperventilation-induced seizure activation is a commonly used approach in electroconvulsive therapy (Datto et al., 2002; Haeck et al., 2011; Loo et al., 2010) or in the assessment of epilepsy (Abubakr et al., 2010; Jonas et al., 2011; Tsiptsios et al., 2010), we have very little mechanistic insight into how hyperventilation causes the seizures. It is generally believed that the seizure induction and duration relate to the degree of hypocapnia (Bergsholm et al., 1984), but when it comes to the existing data, the relationship between the level of hypocapnia and seizure activity is not always straightforward (Wirrell et al., 1996). Thus, the induction of epilepsy may in part be neurogenic. Indeed, it has been suggested that hyperventilation-induced mesiotemporal epilepsy and panic disorders may share common neurobiological mechanisms that involve maladaptive amygdalar activation (Gerez et al., 2011; Yang et al., 2011).

This review discusses the neuronal and ventilatory functions controlled by breathing and we evaluate to what extent brain states interact in a reciprocal manner with the neuronal networks that control breathing. For obvious reasons, it is impossible to cover the entire field of neuronal and ventilatory control of breathing in one review. Thus, at the outset of this review, we would like to emphasize that we do not attempt to provide a complete overview of the various neuronal mechanisms associated with breathing. Instead, we focus on some specific, yet fascinating, examples with a special emphasis on the generation of the sigh.

The sigh is a deep augmented breath with distinct neurobiological, physiological, and psychological properties that distinguish it from a normal eupneic breath. Sighs are typically

triggered by a normal eupneic breath and are followed by a respiratory pause, which is referred to as "postsigh apnea." Figure 1 shows the respiratory trace of a typical sigh with its two distinct components (Fig. 1): a normal eupneic breath, triggering the large-amplitude sigh, followed by the postsigh apnea (Fig. 1). Under certain conditions, the sigh can become uncoupled and independent from eupneic activity (Lieske et al., 2000). Sighs have important ventilatory functions as they lead to a maximal expansion of the lungs, which prevents the progressive collapse of alveoli (atelectasis) (Bendixen et al., 1964; Cammarota et al., 2011; Hess and Bigatello, 2002; Hoch et al., 1998; Koch et al., 2012).Sighs also restore lung compliance (Caro et al., 1960; Ferris and Pollard, 1960) and maintain normal lung function (Cherniack et al., 1981). Genetically engineered mice that are unable to sigh eventually die of major lung problems (Koch et al., 2012), suggesting that sighs are essential for survival. Because of the large tidal volume associated with sighs and the ability to maximally expand the lung, sighs are often referred to as "augmented breaths." But in this review, we want to emphasize that the sigh is not just a breath that is augmented. Sighs have distinct nonventilatory, behavioral functions that go well beyond a simple role in augmenting lung volume. Indeed, sighs have inspired philosophers, musicians, and poets for several centuries. "Sigh no more, Ladies" is a famous poem by William Shakespeare, and Johann Sebastian Bach (1685–1750) expresses in his cantata BWV13: "Meine Seufzer, meine Tränen" (my sighs, my tears) or the chorale BWV 254: "Ach Gott, erhör mein Seufzen und Wehklagen" (Oh god, listen to my sighs and cries of despair).

In contrast to the artists' early understanding of the deeper nature of the sigh, scientists have largely overlooked the behavioral role of sighing. One of the first behavioral characterizations of the sigh in the scientific literature was made by Haldane et al. (1919). These authors described that the frequency of sighing changes during the transition from sitting to lying. The relative lack of interest in the behavioral role of the sigh in the early scientific literature is somewhat surprising, given that sighs are not a rare breathing behavior. Sighs occur spontaneously, and babies sigh every few minutes (Fig. 2A; Fleming et al., 1984; Hoch et al., 1998), while adults continue to sigh regularly, albeit at a lower frequency (Bell et al., 2011; Vlemincx et al., 2009, 2011, 2013a). Indeed, sighs can occur at surprisingly regular intervals (Fig. 2A). In its extreme, some patients have the irrepressible persistence of sighing. Before the occurrence of irrepressible sighing, a large proportion of such patients seem to experience a traumatic event or anxiety (Sody et al., 2008). However, so far there has been no attempt to mechanistically explain a possible relationship between a traumatic event and the occurrence of a "sigh syndrome." Indeed, the search for the term "sigh syndrome" yields only this one publication (Sody et al., 2008).

Nonetheless, it would be wrong to conclude that nothing is known about sighs. We can trust that Shakespeare already knew that sighs are not just augmented breaths and that it would be misleading to state: "No more augmented breaths, ladies." In the following sections, we review distinct behavioral functions for the sighs and their behavioral consequences in health and disease.

2 SIGHS MAY SIGNAL CHANGES IN BEHAVIORAL STATE

In a pioneering study by Soltysik and Jelen (2005), the authors demonstrate that sighs have important roles in the body language repertoire of rodents. A safety stimulus signaling to the animal that they will not be exposed to a tail shock leads to a 20-fold increase in sighing. Thus, sighs are specifically expressed during the emotional state of relief, and sighing was even contagious. The authors hypothesize that the sigh could act as a social signal of safety, which is a signal opposite to the alarm cry. It is easy to conclude that sighs may have a similar role in humans. Humans communicate emotional states by smiling, laughing, frowning, and weeping (Teigen, 2008), and the so-called sigh of relief certainly belongs to this family of behaviors (Vlemincx et al., 2009, 2010a). But the behavioral role of sighs goes beyond the sigh of relief. We have all experienced the "sigh of love," yet sighs are not associated only with positive emotions. Sighs are also generated during negative emotions such as panic (Abelson et al., 2001), distress, sadness, or despair as expressed in the music by Johann Sebastian Bach ("my sigh, my tears," BWV13, "god listen to my sighs and cries of despair," BWV254).

In general terms, sighs could signal a behavioral state change: For example, in the "sigh of relief," sighs signal the change from fear to relaxation. Teigen (2008) also describes situations in which sighs are elicited by a quick drop in physiological arousal, during situations in which humans feel helpless and surrender. The above-mentioned statements by Johann Sebastian Bach could also fall into this category.

The hypothesis that sighs are generated in association with changes in brain states is also consistent with known changes in the sleep/wake cycle. Sighs are frequently generated during the transition from wakefulness to NREM sleep, or from sleep to arousal (Eckert et al., 2007; Orem and Trotter 1993). Based on the tight association with state changes, Orem and Trotter (1993) concluded that the generation of sighs is likely controlled by centrally mediated mechanisms. The concept of a centrally mediated mechanism contrasted the hypothesis that sighs constitute a simple reflex caused by lung hyperinflation, an idea that has prevailed for several decades (Bartlett, 1971; Glogowska et al., 1972; Thach and Taeusch, 1976; Wulbrand et al., 2008). Nevertheless, the concept of a central origin of sighs is consistent with the observation that sighs persist following deafferentation (vagal nerve denervation) in *in vivo* cats (Cherniack et al., 1981), following lung transplantation in humans (Shea et al., 1988), and following complete deafferentation when isolated in an *in vitro* preparation as discussed later in the review (Figs. 1B and 2D; Lieske et al., 2000).

3 SIGHS AND THE CONTROL OF AROUSAL

Glogowska and collaborators (1972) were perhaps the first to report that sighs are triggered by stimuli that initiate arousal. Subsequently, McGinty and coworkers (1979) described in detail a stereotypic sequence of events in which the generation of sighs is associated with increased somatic activity, variable heart rate deceleration, and sleep state transition. This observation was confirmed in a series of elegant studies demonstrating that in infants, arousal begins with the occurrence of a sigh (i.e., augmented breath), followed by thrashing, eye opening, and repositioning of the head (Lijowska et al., 1997; McNamara et al., 1998).

Interestingly, the same stereotypical sequence of behaviors was observed under different conditions (McNamara et al., 1998; Thach and Lijowska, 1996). Spontaneously occurring sighs can be associated with arousal in the absence of an obvious sensory stimulus (Anderson et al., 1996; Thach and Lijowska 1996), but sighs followed by arousal could also be triggered mechanically (McNamara et al., 1998; Thach and Lijowska, 1996). Perhaps most importantly, sighs can also be triggered by changes in blood gases, as the generation of the sigh is particularly sensitive to hypoxic challenges (Bartlett, 1971; Bell and Haouzi, 2010; Bell et al., 2009; Cherniack et al., 1981; Hill et al., 2011; Lieske et al., 2000; Schwenke and Cragg, 2000). This chemical sensitivity is in part mediated centrally and does not even require peripheral chemoreceptors (Hill et al., 2011; Lieske et al., 2000). The intrinsic chemical sensitivity becomes highly significant in the context of arousal, as it is a protective mechanism that alerts an individual when exposed to potentially dangerous hypoxic and hypercapnic conditions. A specific example is sleeping babies lying with their face down (prone position). The prone position will lead to a buildup of CO_2 and a decrease in inspired O_2 (Bolton et al., 1993; Chiodini and Thach, 1993; Kemp and Thach, 1991; Kemp et al., 1993). This hypercapnic/hypoxic challenge evokes sighs, followed by arousal and head turning, which ultimately ameliorates the conditions that endanger the sleeping infant (Lijowska et al., 1997; McNamara et al., 1998). Thus, the generation of the sigh is a central nervous system mechanism that is not only temporarily associated with changes in brain states but also seems to be instrumental in initiating both subcortical and cortical arousals. Consequently, one can conclude that the sigh is an essential central nervous system adaptation that responds to changes in blood gases and initiates a series of events that lead to an arousal response, which will refresh the inspired O_2 supply of the infant (Ayas et al., 2000; Fewell, 2005; Horne et al., 2005; Lijowska et al., 1997; Masa et al., 2003; McNamara et al., 1998; Parslow et al., 2003; Thach, 2002).

4 SIGHS AND THEIR IMPLICATIONS FOR SIDS AND OTHER PATHOLOGIES

The stereotypical response from respiratory distress associated with the prone position protects a healthy child, but may fail in children that later died of SIDS. Prospective studies have shown that spontaneous and induced arousals during sleep are decreased in SIDS victims (Dunne et al., 1992; Kahn et al., 1992; Kato et al., 2006; McCulloch et al., 1982; Sawaguchi et al., 2005; Schechtman et al., 1992). An important aspect of this behavioral sequence is the coupling between the respiratory behavior and heart rate control. Indeed, one of the hallmarks of sighs is their association with an initial heart rate increase, which is followed by a heart rate decrease (Fig. 3; Haupt et al., 2012; McNamara et al., 1998; Porges et al., 2000; Weese-Mayer et al., 2008a; Wulbrand et al., 2008). This sigh-coupled heart rate change not only seems to be important for coordinating cardiorespiratory function but also correlates with the degree of cortical arousal (Thach, 2002; Thach and Lijowska, 1996). Infants that later died of SIDS had a lower heart rate variability during a sigh (Franco et al., 2003). This is interesting, since lower heart rate variability is typically associated with higher parasympathetic tone, a sign of dysautonomia.

Although not all studies report a difference in sigh generation (Franco et al., 1998; Kahn et al., 1992; Kato et al., 2001), there is some evidence suggesting that SIDS victims exhibit significantly fewer sighs (Kahn et al., 1988). Interestingly, one report suggests that infants

sigh more often in prone than in supine position. Yet, the children that later died of SIDS had less arousal even though prone position was more frequent, suggesting that the coupling between the sigh and arousal may have been disturbed (Groswasser et al., 2001; Kahn et al., 1992). Thus, a genetic predisposition or any condition that blunts the initiation or effectiveness of this arousal sequence may convey an increased risk for SIDS (Franco et al., 2010; Garcia et al., 2013).

An abnormal cardiovascular–respiratory coupling associated with the sigh may also have detrimental consequences in a variety of other human disease states. An attenuated response to endogenous sympathetic stimulation following a sigh has been reported in congenital hypoventilation syndrome (CCHS) (O'Brien et al., 2005), and an increased sympathetic activation has been reported in children with sleep-disordered breathing (O'Brien and Gozal, 2005). Disturbances in cardiorespiratory coupling are also characteristic of familial dysautonomia and sickle-cell anemia (Sangkatumvong et al., 2011; Weese-Mayer et al., 2008a). In sickle-cell anemia, the frequency of sighs is not different from controls, but sighs are much more likely to induce pronounced perfusion drops that are presumably associated with an exaggerated sympathetic and suppressed parasympathetic response. Hypoperfusion in sickle-cell anemia is a particularly dangerous situation, because it could lead to red blood cell polymerization followed by a vaso-occlusive crisis (Platt et al., 1994; Sangkatumvong et al., 2010, 2011). Indeed, the sigh-triggered hypoperfusion may be responsible for the sudden death that occurs frequently in this patient population (Sangkatumvong et al., 2011).

The sigh may also have an important role in obstructive sleep apnea, specifically during the recovery from an airway obstruction (Alvarez et al., 1993; Ramirez et al., 2013a; Wulbrand et al., 1998). The termination of airway occlusion is typically abrupt and associated with a sudden burst of genioglossus activity (Berry and Gleeson, 1997; Rees et al., 1995; Remmers et al., 1978; Wulbrand et al., 1998, 2008) and the recruitment of phasic inspiratory motor units (Wilkinson et al., 2010). Reflex recruitment of pharyngeal dilator muscles seems to be insufficient for this abrupt response, and central mechanisms that stage the initiation of arousal become important. As similarly described above in the context of SIDS, arousal is stimulated by the increasingly hypoxic and hypercapnic conditions associated with the airway occlusion (Berry and Gleeson, 1997; Gleeson et al., 1990; Kimoff et al., 1994). Although cortical arousal is not always observed following airway occlusion, sighs consistently coincide with subcortical arousal involving a sudden rise in limb motor activity and a distinct neck extension, an adaptive response that can contribute to the termination of an airway occlusion (Perez-Padilla et al., 1983; Wulbrand et al., 2008).

5 SIGHS HOMEOSTATICALLY RESET BREATHING VARIABILITY

The previous sections suggest that (a) sighs signal state changes and (b) sighs can trigger arousal. But there may be a third, equally important function for sighs. Based on a series of fascinating human psychophysiological studies, Vlemincx and coworkers (Vlemincx et al., 2010b, 2013a; Wuyts et al., 2011) proposed the intriguing hypothesis that the sigh acts as a psychophysiological mechanism that resets eupneic breathing variability associated with different psychological states. Indeed, a high degree of breathing variability is normal (Donaldson, 1992; Mangin et al., 2011; Small et al., 1999; Tobin et al., 1995; Wuyts et al.,

2011; Wysocki et al., 2006). This variability is adaptive as it allows the respiratory network to sensitively react to changes in environmental and behavioral demands (Wuyts et al., 2011). Speech, for example, requires extensive variability in respiratory control (Ghazanfar and Rendall, 2008; Loucks et al., 2007). This variability, however, is not random. Long sentences follow large-amplitude breaths, and the timing of individual breaths is associated with the syntax of spoken sentences. Disturbances in respiratory control can lead to dysarthria, which summarizes different forms of speech disorders (Enderby, 2013; Liegeois and Morgan, 2012). Patients suffering, for example, from Parkinson's disease take a greater percentage of breaths at locations that are unrelated to a syntactic boundary, suggesting that the interaction between cognition and respiratory timing is disturbed in this patient population (Brown and Marsden, 1990; Huber and Darling, 2011; Huber et al., 2012). Thus, respiratory variability, which is highly controlled in healthy speech, can become random in a variety of disorders.

Under healthy conditions, increased respiratory variability characterizes, for example, laughter, when abrupt decreases in inspiratory timing are typical (Boiten, 1998; Boiten et al., 1994). But respiratory variability can also decrease, for example, during sustained attention tasks (Vlemincx et al., 2011). Upon completion of the attention task, breathing variability increases again and the sigh rate increases (Vlemincx et al., 2011). According to the hypothesis by Vlemincx and coworkers (2013a), sighs reinstate normal, healthy variability during increased or after decreased variability (Vlemincx et al., 2011). Indeed, the authors can demonstrate that random unstructured variability increases before a sigh and decreases following a sigh (Vlemincx et al., 2010a,b). Thus, this concept attributes a critical homeostatic role to the sigh.

Consistent with this homeostatic hypothesis is the observation that sighs typically terminate periods of irregular breathing in an animal model (Orem and Trotter, 1993). In these experiments, sighs were also associated with changes in body position, which is consistent with their role in monitoring changes in behavioral state and arousal (Orem and Trotter, 1993). We conclude that sighs function as (a) a homeostatic resetting mechanism, (b) a monitor for brain state changes, and (c) a mechanism that induces arousal.

6 WHEN SIGHS ENHANCE BREATHING VARIABILITY AND INDUCE HYPERAROUSAL

While the combination of the above-mentioned properties is adaptive and essential in healthy subjects, sighs could also turn into major drivers of certain human disease states. For example, patients with panic disorder suffer from significantly increased respiratory variability and hyperventilation (Abelson et al., 1996, 2001, 2008; Martinez et al., 2001; Meuret et al., 2001; Roth et al., 2002; Wilhelm et al., 2001a,b). Their breathing irregularity persists even when panic is pharmacologically controlled, indicating that respiratory dysregulation is not secondarily induced by the panic attack but may convey panic attack vulnerability (Abelson et al., 1996, 2001, 2008). Klein suggested that hypercapnia causes a dysregulation of brainstem circuits that drive suffocation fears, which in turn will evoke panic attacks (Gorman et al., 1994; Klein, 1993, 1994; Martinez et al., 2001). He specifically hypothesizes that an episodic dysfunction in endogenous opioidergic regulation involving

the same brainstem areas that also regulate breathing is responsible for panic disorder (Klein, 1993; Preter and Klein, 2008). Consistent with brainstem dysfunction is the observation that patients suffering from CCHS are not only unable to sense CO_2 but also significantly less anxious than controls (Pine et al., 1994).

Alternatively, excessive random breathing variability in panic disorder patients may centrally activate sighs possibly in a physiological attempt to reduce and reset this pathological variability. Indeed, patients with panic disorders typically show increased sigh frequency (Abelson et al., 2001; Schwartz et al., 1996; Vlemincx et al., 2013a). However, instead of regularizing variability as is the case in healthy subjects, the increased generation of the sighs may exaggerate the already existing breathing variability by further increasing tidal volume variability, which is a characteristic feature of patients with panic disorder (Abelson et al., 2001; Schwartz et al., 1996; Wilhelm et al., 2001a,c). Sighs could further increase irregularity through the so-called postsigh apnea, which can create conditions of intermittent hypoxia and oxidative stress if sighs occur frequently (Garcia et al., 2013; Ramirez et al., 2013a,b). Consistent with the notion that sighs are centrally generated is a report suggesting that sighs in panic disorder patients are not triggered by a pCO_2-dependent chemical stimulus (Abelson et al., 2001). Interestingly, rats bred for high anxiety showed a significantly different breathing behavior with an increased number of sighs when compared to rats bred for low anxiety (Carnevali et al., 2013) further supporting the notion that anxiety and the generation of sighs are centrally linked. Assuming that sighs have also arousal-promoting functions, what follows is that excessive sighing may generate a hyperarousal state, which could exaggerate panic.

Hyperarousal is a characteristic feature of several forms of panic disorders (Ottaviani et al., 2012) and disorders associated with anxiety. Examples are posttraumatic stress disorder (Edmondson and Cohen, 2013; Perez et al., 2012), attention deficit hyperactivity disorder (Antshel et al., 2013; Hanson et al., 2012), general anxiety disorder (Brunet et al., 2013; Hoge et al., 2013), insomnia (Hantsoo et al., 2013; Killgore et al., 2013; Vincent and Walsh, 2013; Wallhausser-Franke et al., 2013), and Fragile X syndrome (Berry-Kravis et al., 2012; Heilman et al., 2011). Autonomic dysregulation is an aspect of some of these disorders, but sighs have not been specifically characterized in these disorders, (Beauchaine et al., 2007; Heilman et al., 2011; Kalk et al., 2011; Musser et al., 2013).

The pathway to an anxiety disorder may begin in a healthy human: homeostatic mechanisms continuously establish a dynamic balance between breathing stability and instability (Vlemincx et al., 2013a,b). In an arithmetic task, an increased sigh frequency may be adaptive in decreasing variability (Vlemincx et al., 2011), but it might also temporarily induce a hyperarousal state. A heightened arousal state could initially be adaptive as it stages the healthy flight-and-fight response. In the example of an infant sleeping in a prone position, this response is essential for survival. However, a heightened arousal state will eventually become maladaptive in chronic worriers. As a result of the chronic nature, these worries may become pathological leading to exaggerated cardiac defense responses, reduced sinus-arrhythmia (Vila et al., 2007; Vlemincx et al., 2013a), and reduced parasympathetic activity which is typical for chronic worriers (Thayer and Brosschot, 2005; Thayer et al., 1996; Vlemincx et al., 2013a,b). Constant worrying and chronic anxiety may also lead to

insomnia as frequent arousals may contribute to sleep fragmentation. Anxiety and insomnia are closely related clinical entities (Brown et al., 2013; Dong et al., 2013; Lee et al., 2013). This relationship could be associated with an increased propensity to sigh, a possibility that deserves further investigations.

The above considerations suggest that panic disorders emerge through an imbalance between the cardiorespiratory and arousal system. A physiological, homeostatically controlled cardiorespiratory-coupled flight-and-fight response could become maladaptive and homeostatically uncontrolled in a chronic state. This hypothesis may apply not only to panic disorder but also possibly to many disorders associated with heightened anxiety. But unfortunately, in many of these disorders, the roles of the underlying cardiorespiratory characteristics and the sigh have not been explored.

7 THE PRE-BÖTZINGER COMPLEX, AN ESSENTIAL BRAIN REGION FOR THE GENERATION OF THE SIGH AND EUPNEIC ACTIVITY

Neurobiological correlates for many of these considerations can be found at multiple levels of the CNS. For example, “balanced amygdala activation” in response to fearful stimuli may turn into reduced amygdala activation, as is characteristic for panic disorders (Ottaviani et al., 2012), or into a hyperactive amygdala, which would be equally maladaptive. But before discussing these wider network interactions, we would like to focus on the question of how breathing and sighing are generated within the CNS, as this is at the core of this review.

The French physiologist Pierre Flourens (1794–1867) first proposed that breathing is generated within a very specific region of the brainstem, located in the medulla oblongata. He called this region the “noeud vital” to indicate its vital importance for life (Flourens, 1858). But it was not until another 130 years had passed that Smith et al. (1991) confirmed Flourens’ proposal. Smith et al. discovered not only that lesioning a very specific area within the ventrolateral medulla of neonatal rats abolishes respiratory activity, but also that brainstem slices that contain this area continue to spontaneously generate respiratory activity in isolation. Smith and coworkers (Smith et al., 1991) termed this critical area the “pre-Bötzinger complex” (preBötC) (Fig. 2B and C; Schwarzacher et al., 2011). Located within the same plane of the slice is the hypoglossus motor nucleus (XII), which continues to be rhythmically activated by the preBötC. The XII continues to generate rhythmic motor activity (Telgkamp and Ramirez, 1999) that can be recorded from the XII rootlets (Smith et al., 1991). Since in intact animals, including humans, the XII is activated in phase with inspiration (Ramirez et al., 2013a; Withington-Wray et al., 1988), it is assumed that the rhythmic activity in the slice represents fictive inspiration. This discovery provoked controversies that began in 1991 and continue to this day. A major reason for these controversies was the long-held dogma that different forms of breathing are generated in different brain centers. To this day, some Physiology textbooks teach that breathing (eupneic activity) is generated in the pneumotactic center located within the pons, whereas gasping is generated in a gasping center located within the medulla, as originally proposed by Lumsden (1923). Indeed, the ensuing controversy centered around the question whether the preBötC is the gasping center or a network critical for generating eupneic activity. A series of studies employing various molecular, genetic, and pharmacological tools unambiguously confirmed

that even in fully intact adult animals of different species, the preBötC is, indeed, the noeud vital, that is, the center of life that is essential for eupneic breathing (Gray et al., 2001, 2010; Ramirez et al., 1998; Tan et al., 2008). Surprisingly, the location of a "sigh" center was never discussed, possibly because most respiratory physiologists considered the sigh simply as a bigger, that is, "augmented breath" that did not require a separate center.

8 THE CONCEPT OF NETWORK RECONFIGURATION

In 2000, Lieske and coworkers discovered that the network isolated in the pre-Bötzinger generates not just one type of respiratory activity but three distinct, qualitatively and quantitatively different, respiratory activity patterns (Lieske et al., 2000). Lieske et al. (2000) proposed that these three activities constitute the neuronal basis for (a) eupneic (Fig. 4), (b) sighing (Figs. 1B and 2B, D), and (c) gasping activity. This discovery was conceptually a major departure from the long-held belief that different regions of the brain are responsible for the generation of different respiratory patterns (Lumsden, 1923). To explain their finding, (Lieske and coworkers, 2000) introduced the concept of network reconfiguration to the respiratory system and postulated that the preBötC can assume different network states that give rise to eupneic, gasping, and sighing activity depending on the oxygenation and neuromodulatory milieu of the network. Experiments performed several years later confirmed the concept of network reconfiguration in more intact preparations.

The concept of network reconfiguration also provided an explanation for how different regions of the brain interact within the wider respiratory network: as many areas within the CNS will reconfigure the respiratory network and vice versa, the respiratory network will reconfigure other areas of the nervous system. From the behavioral perspective, the preBötC is not the only region that participates in breathing. Additional areas can be found in the medulla, the pons, the cerebellum, the cortex, the amygdala, the hypothalamus, and the periaqueductal gray (PAG) (Brannan et al., 2001; Burdakov et al., 2013; Chamberlin and Saper, 1994; Liotti et al., 2001; Masaoka et al., 2012; Nattie and Li, 2012; Ramirez et al., 2012; Smith et al., 2009; Subramanian and Holstege, 2013). The contribution of each of these areas adds different and important aspects to the neuronal control of breathing making breathing one of the most modulated and complex behaviors. As already mentioned, every spoken word in humans is a breathing behavior that emerges through a complex cortical and subcortical orchestration of numerous network interactions (Holstege, 1989; Subramanian and Holstege, 2009, 2013; Subramanian et al., 2008; VanderHorst and Holstege, 1996). In some disorders, such as in Parkinson's disease, disturbances in language will result from the dysregulation of the complex, reciprocal interactions between cognitive and respiratory functions (Altmann and Troche, 2011; Kemmerer et al., 2013; Skodda, 2011). Similarly, anxiety and panic will be the result of complex interactions between the respiratory network and a variety of areas including the amygdala, hypothalamus, and neocortex (Abelson et al., 2008; Frysztak and Neafsey, 1991; Nattie and Li, 2012). Thus, behaviors associated with breathing depend on the reciprocal interactions between the preBötC and other brainstem areas, such as Kölliker-Fuse in the pons, the RTN/pFRG, and the Bötzinger complex in the medulla, as well as numerous subcortical and cortical areas. There are various areas that can trigger an apnea when lesioned (Song et al., 2010), but the preBötC remains the only area that is not only essential for breathing but also continues to generate three distinct

respiratory activities in isolation (Gray et al., 2010; Lieske et al., 2000; Smith et al., 1991; Tan et al., 2008). Thus, any discussion of how different areas influence or are influenced by breathing or the sigh needs to include this noeud vital.

9 HOW IS BREATHING VARIABILITY GENERATED?

As discussed earlier, breathing variability is an essential behavioral property that needs to be homeostatically regulated (Wuyts et al., 2011). Variability is adaptive as it allows the respiratory network to sensitively and quickly react to changes in environmental and behavioral conditions. Thus, how does the nervous system accomplish the important task of generating rhythmic activity patterns that are stable, yet also very flexible and at times extremely variable? In this review, I propose that the neuronal basis of breathing variability and stability is deeply rooted within the synaptic interactions and intrinsic membrane properties of this relatively small neuronal network. This proposal rejects several misconceptions that have confused the field over several decades. An overarching misconception that drove much of the gasping controversy was the notion that the preBötC operates like a simple, hard-wired “clock” or “pacemaker network,” a view that is difficult to reconcile with the enormous variability, flexibility, and plasticity that is required for adaptive and variable eupneic breathing. Sections 9.1–9.5 illustrate why the preBötC is not a simple hard-wired pacemaker network or clock.

9.1 Respiratory Pacemaker Neurons Are Not a Sign of a Primitive Rhythm Generating Network

With the discovery of the preBötC came the demonstration that this network contains autonomously bursting rhythmic neurons that are referred to as “bursting pacemakers” or simply “pacemakers” (Smith et al., 1991). The presence of pacemaker neurons was later confirmed in numerous studies (Johnson et al., 1994; Pena et al., 2004; Thoby-Brisson and Ramirez, 2000; Tryba et al., 2008; Viemari and Ramirez, 2006; Viemari et al., 2011; Fig. 5). These neurons intrinsically generate rhythmic activity much like the cardiomyocytes in the heart (Bradd et al., 2012; Fenske et al., 2011; Sirenko et al., 2013). The demonstration of pacemaker neurons was interpreted by some as a special attribute of a simple rhythm generating gasping network that misses much of the flexibility of eupneic breathing. Perhaps some of this misinterpretation came from the fact that neurons with very similar bursting properties have previously been demonstrated in numerous invertebrate networks (Graubard and Hartline, 1991; Harris-Warrick, 2002; Russell and Hartline, 1978; Soto-Trevino et al., 2005). But this was another misconception, because in invertebrate networks also, pacemaker neurons are everything but simple (Hobbs and Hooper, 2008; Prinz et al., 2003; Ramirez and Pearson, 1991a,b, 1993; Rinberg et al., 2013). Moreover, within the mammalian nervous system, pacemaker neurons are not unique to the respiratory network, and are found in many areas of the CNS; some of these networks are concerned with complex higher functions (Brocard et al., 2013; Kolta et al., 2010; Llano and Sherman, 2009; Marcuccilli et al., 2010; Martell et al., 2010, 2012; Mrejeru et al., 2011; Ramcharan et al., 2005; Ramirez et al., 2004; Ziskind-Conhaim et al., 2010). Indeed, there is probably no region in the mammalian brain that does not contain pacemaker neurons (Ramirez et al., 2011).

9.2 Pacemaker Neurons Do Not Discharge in a Metronome-Like Manner

The word “pacemaker” may imply to some that these neurons function like a clock and pace a network rhythm in a metronome-like manner. But this is not the case. The discharge of these neurons is variable and highly plastic (Carroll and Ramirez, 2013). In any given neuron, the discharge is determined by a variety of outward, inward, and leak currents (Del Negro et al., 2002). Some of the inward currents are burst-promoting such as the calcium-activated nonspecific CAN (Fig. 5A) or the persistent sodium current (Fig. 5B). However, the complement of these currents varies, and every individual neuron establishes a different dynamic balance of inward and outward currents, a principle that has been well documented for invertebrate neurons (Hudson and Prinz, 2010; Khorkova and Golowasch, 2007; Soofi et al., 2012; Temporal et al., 2012; Zhao and Golowasch, 2012). As a result, some neurons within the respiratory network are more bursting than others; some burst regularly, some are irregular, some discharge tonically, and some are silent (Carroll and Ramirez, 2013; Garcia et al., 2011; Koch et al., 2011; Ramirez et al., 2011, 2012; Viemari and Ramirez, 2006). Bursting depends more on the CAN current in some neurons (Fig. 5A) and on the INap current in others (Fig. 5B; Pena et al., 2004; Thoby-Brisson and Ramirez, 2001), and occasionally respiratory neurons are found that depend on the L-type calcium current (Pena, F. and Ramirez, JM, unpublished data). As a population, the intrinsic activities of preBötC neurons span a continuum that covers the entire spectrum from silent to tonic to bursting activities (Carroll and Ramirez, 2013). This has been quantitatively demonstrated for the intrinsic activities of hundreds of neurons recorded in the preBötC (Fig. 6; Carroll and Ramirez, 2013). Thus, the long-held assumption that the respiratory network contains distinct and concrete, hard-wired populations of pacemaker and non-pacemaker neurons needs to be revisited.

9.3 Intrinsic Discharge Properties of any Given Respiratory Neuron Are Plastic

Whether a pacemaker neuron bursts and if it does, how it does so is not established by a fixed genetic program. It is determined by the balance of inward and outward currents, the various receptors, and second messenger systems and to a large extent also by its modulatory and synaptic environment. Neuromodulators released endogenously can induce (Fig. 6A), inhibit, and significantly alter bursting properties in respiratory neurons (Dekin et al., 1985; Doi and Ramirez, 2010; Pena and Ramirez, 2002, 2004; Ptak et al., 2009; Ramirez et al., 2011, 2012; Tryba et al., 2008; Viemari et al., 2011; Fig. 6B). This principle has been well documented in a variety of invertebrate (Crisp et al., 2012; Dickinson and Nagy, 1983; Khorkova and Golowasch, 2007; Ramirez and Pearson, 1991a,b; Zhao and Golowasch, 2012) and other mammalian networks (Kolaj et al., 2007; Mrejeru et al., 2011; Tsuruyama et al., 2013). Within the respiratory network, multiple neuromodulators, such as serotonin, norepinephrine, acetylcholine, or substance P,can alter the distribution of these activities (Doi and Ramirez, 2008; Ramirez et al., 2012; Fig. 6). These neuromodulators target different receptor subtypes, G-proteins, and second messenger systems that will differentially affect the balance between the different inward and outward currents, resulting in a different distribution of these discharge patterns. As an example, norepinephrine acting on the alpha 1 receptor will increase the number of neurons that burst based on the CAN current (Viemari and Ramirez, 2006). But, multiple neuromodulators converge simultaneously onto multiple second messenger systems and G-proteins, which imbue every

single neuron within the respiratory network with an enormous flexibility and plasticity (Doi and Ramirez, 2008). The example shown in Fig. 6B demonstrates that the same neuron at the single-cell level can burst in different intrinsic modes, which is reminiscent of the different modes of the network (Fig. 7; Tryba et al., 2008). Indeed, the modulatory effects at the cellular level have important functional consequences at the network level. Norepinephrine acting, for example, on the ICAN current at the level of the single neuron will affect the shape and amplitude of inspiratory activity at the network level, whereas norepinephrine acting on the INap current at the cellular level will affect the respiratory frequency at the network level (Viemari and Ramirez, 2006). Thus, by acting on different receptor subtypes, G-protein-coupled receptors, and different second messenger systems, neuromodulators have an almost unlimited capability to orchestrate intrinsic membrane properties of respiratory neurons and thereby alter different parameters of respiratory activity. These changes can occur not only at the level of intrinsic membrane properties, but modulatory effects will also target synaptic transmission adding another layer of complexity to the respiratory network. Both intrinsic and synaptic properties will engage in a complex interplay that largely depends on the modulatory state (Doi and Ramirez, 2008; Koch et al., 2011; Ramirez et al., 2011,2012).

9.4 The Modulatory State of the Respiratory Network Is Plastic

Indeed, the modulatory state of the respiratory network is determined by multiple modulators released not only from neurons intrinsic to the network but also from neuromodulators that are released from neurons converging onto the respiratory network from numerous other brain regions. Prominent areas include the hypothalamus, the locus coeruleus, and the raphe nucleus (Doi and Ramirez, 2010). But there are many additional areas that play critical roles under different behavioral, developmental, and environmental conditions. Thus, the modulatory milieu at the network level is not static but defined by the changing behavioral and environmental conditions that the organism encounters or generates. A sleeping animal is defined by a different modulatory state than a waking animal, and different sleep states are characterized by different modulatory states. Whether an animal is anxious, panicking, quiet, concentrated, hypoxic, or hypocapnic will all be reflected in different modulatory states that will directly impact the neuronal discharge properties of the single neurons, and their synaptic interactions at the population level.

9.5 Respiratory Neurons Discharge in a Variable Manner Within the Respiratory Cycle

Many computational models assume that respiratory neurons can be classified into a relatively small number of concrete classes of neurons that fire at a fixed time in relation to the respiratory cycle. A recent unexpected discovery suggests that the phase-locked rhythmic activation of respiratory neurons within the preBötC forms a continuum between the different neuron types (Fig. 8-I; Carroll and Ramirez, 2013; Franco et al., 2003, 2010). This continuum consists of neurons that discharge very early, somewhat early, throughout the cycle, somewhat late or very late during inspiration (Fig. 8-I). Some neurons discharge during expiration, or during postin-spiration; some neurons discharge in a ramp-like, bell-shaped, or decrementing manner (Carroll et al., 2013). Moreover, there is remarkable onset variability (Fig. 8-II). Bursting and nonbursting neurons can lead some respiratory cycles, but follow others. This finding leads to the conclusion that the respiratory network is

stochastically assembled in a cycle-by-cycle manner (Carroll and Ramirez, 2013; Carroll et al., 2013). In other words, every breath is a new breath with regards to the underlying neuronal mechanisms. Thus, breathing variability is an intrinsic property that is build into the very mechanisms that govern respiratory rhythm generation within the core respiratory network. Based on computational modeling, this variability may be achieved through a sparse connectivity between respiratory neurons (Carroll and Ramirez, 2013). The study by Carroll and Ramirez (2013) compared the onset variability with different degrees of sparse connectivity and found that the higher the onset variability increased, the sparser was the connectivity.

However, it is important to emphasize that the individual onset variability does not imply that the overall network output must be irregular. Indeed, the rhythmic activity that emerges through this ensemble is regular and stable, yet very flexible (Carroll and Ramirez, 2013). This study also showed that the larger the number of sparsely connected neurons is, the more regular the rhythmic output becomes. At every given moment, it is possible to alter the activation and synchronization of the neuronal elements that give rise to the respiratory activity. However, the sparse connectivity and the multitude of modulatory processes that determine respiratory activity may be at the limits, the price to pay to maximize flexibility. It is conceivable that mechanisms that reduce excitatory synaptic transmission or enhance bursting properties could easily destabilize the network, which could drive the network into random variability. The generation of the sigh is an ideal cellular mechanism to reset this network ensemble. The majority of respiratory neurons within the preBötC are simultaneously activated during the sigh and become simultaneously inhibited after the sigh, giving rise to the postsigh apnea (Fig. 2; Lieske and Ramirez, 2006a,b; Lieske et al., 2000; Orem and Trotter, 1993; Tryba et al., 2008). Thus, the sigh is a neuronal event that supra-maximally activates simultaneously many neurons within the respiratory network. Future experiments will need to test the possibility that this resetting event indeed alters the variability in subsequent cycles at the network level as would be predicted from the hypothesis by Vlemincx and collaborators (Vlemincx et al., 2010b, 2013a; Wuyts et al., 2011).

10 EUPNEIC AND SIGHS ARE GOVERNED BY DISTINCT CELLULAR MECHANISMS

A fascinating, yet unresolved, question is how the preBötC can simultaneously generate two distinct respiratory activities—eupneic and sigh activity within the very same network using the same neurons (Lieske et al., 2000). As stated earlier, the majority of neurons are activated during both eupneic and sigh activity, and this overlap may even be a prerequisite for the hypothesized role of the sigh in resetting the ongoing eupneic network activity. Yet, the timing of eupneic and sigh activities is radically different. One rhythm operates in the range of seconds, the other in a range of several minutes (Lieske et al., 2000). Sigh and eupneic activities also involve different cellular mechanisms. Blockade of PQ-type calcium channels selectively blocks sighs, but not eupneic activity (Lieske and Ramirez, 2006a). The genetic knockout mouse of PQ-type calcium channels continues to breathe but fails to sigh, which is fatal (Koch et al., 2012). Metabotropic glutamate receptors of the subtype 8, group

III are critical for the generation of sighs, but not eupneic activity, and eupneic activity is more sensitive to NMDA-dependent modulation than sigh activity (Lieske and Ramirez, 2006b). Not surprisingly, both rhythms can be independently modulated. Acetylcholine acting on muscarinic receptors activates sighs, but inhibits eupneic activities (Fig. 7; Tryba et al., 2008), while serotonin acting on 5-HT2A receptors (Pena and Ramirez, 2002) and substance P acting on NK1 receptors activate both eupneic and sigh activity (Doi and Ramirez, 2010; Pena and Ramirez, 2004). A differential modulation of sighs and eupneic breathing was also described in response to dorsomedial hypothalamic stimulation (Reynolds et al., 2008). The differential modulation at the neuronal level provides a mechanistic explanation how sighs could be differentially activated in the behaving animal.

11 NEURONAL STRUCTURES AND NEUROMODULATORY MECHANISMS LINKING SIGHS WITH ANXIETY AND AROUSAL

As already mentioned, the amygdala is an important integrator that links emotions and respiration (Freire and Nardi, 2012), and an imbalance in amygdalar activity has been implicated in anxiety and panic disorders (Freire et al., 2013; Nardi et al., 2009). Using an *in vitro* approach, Onimaru and Homma reveal not only strong descending pathways to the respiratory network within the medulla, but also weak ascending pathways from the respiratory network to the amygdala (Fujii et al., 2010, 2011; Onimaru and Homma, 2007). The fact that these ascending pathways are weak is interesting, as this could be a filtering mechanism. Specifically, under control conditions, only sighs that lead to the maximal activation of the respiratory network might be able to activate the amygdala, while inputs associated with normal breathing may be too weak to activate the amygdala. However, at this point, this is pure speculation and probably somewhat simplistic. This is most obvious if one considers a series of elegant human EEG studies that document complex interactions between anxiety and breathing (Masaoka and Homma, 2000). In human subjects feeling anxiety and exhibiting an increased respiratory rate, a positive wave can be triggered from the onset of inspiration, a phenomenon that is called “the respiration-related anxiety potential.” The increase in respiratory rate is related to the anxiety level (Masaoka and Homma, 2000). Moreover, the respiration-related anxiety potential was observed in the right temporal pole in subjects with low anxiety and in the left amygdala in those with high anxiety (Masaoka and Homma, 2000). Patients with lesions in the left amygdala show reduced anxiety levels and respiratory rate during anticipatory anxiety (Masaoka et al., 2003). The authors propose that the left amygdala provides essential excitatory drive to the right amygdala, which is dominantly activated in anxiety (Masaoka et al., 2003).

The amygdala is closely linked with another critical integrator of the limbic response, the PAG. The dorsal PAG, in particular, has a powerful influence on neurons within the preBötC, resulting in tachypnea and hyperventilation (Subramanian, 2013; Subramanian and Holstege, 2013). Interestingly, this area also evokes intense distress, panic terror, and feelings of imminent death, all emotions that are also associated with tachypnea (Del-Ben and Graeff, 2009; Schenberg et al., 2001), but the role in generating sighs has not been specifically investigated. Of clinical interest is that the dorsal PAG also induces the

analgesia associated with stressful situation. In humans, analgesia can be electrically stimulated within the dorsal PAG, but it is also associated with strong aversive reactions.

A third structure critical for linking breathing and emotions is the hypothalamus. The hypothalamus has long been implicated in the fight-and-flight response and the etiology of panic and anxiety disorders (Johnson et al., 2012a; Kuwaki and Zhang, 2012; McDougall et al., 2005; McEwen, 2007; Sherin and Nemeroff, 2011). The perifornical and dorsomedial hypothalamus is particularly interesting as this area releases the neuromodulator orexin (Fig. 9). Orexin mediates wakefulness, arousal, and energy homeostasis (Nattie and Li, 2012). A hypoactive orexin system has been implicated in narcolepsy, whereas a hyperactive orexin system evokes panic and states of anxiety (Johnson et al., 2012a,b). Moreover, these neurons also regulate blood pressure and body temperature (Nattie and Li, 2012). But, orexin neurons from the hypothalamus play also critical roles in the neuronal control of breathing, specifically in the regulation of chemosensitivity, predominantly during wakefulness. Most intriguing, orexin has a strong modulatory role specifically activating sighs: an orexin antagonist decreases the generation of sighs (Nattie and Li, 2012). Thus, in a stress situation, this neuromodulator plays a critical role in orchestrating the flight-and-fight response by activating the cardiorespiratory system and, specifically, by activating sighs as well as arousal. If this neuromodulatory system becomes hyperactive, it would lead to a panic-anxiety syndrome that is manifested in not only the emotional but also the respiratory aspects of this disorder.

Certainly, orexin is only one of many neuromodulators that play a role in staging the flight-and-fight response and anxiety. Other important modulators include neuropeptide Y (Eaton et al., 2007; Giesbrecht et al., 2010), neuropeptide S (Okamura and Reinscheid, 2007; Reinscheid and Xu, 2005), corticotropin-releasing factor (Gilpin, 2012), and angiotensin II (Liu et al., 2012). Acetylcholine involving the hippocampus has also been implicated in anxiety (Mineur et al., 2013; Pandya and Yakel, 2013) and the response to mental stress (Meerson et al., 2010). In this context, it is interesting that the same neuromodulator has strong modulatory effects on the sigh as well (Fig. 7, and see also Fig. 6; Koch et al., 2012; Tryba et al., 2008). Well-studied neuromodulators also include norepinephrine and serotonin, both of which have been implicated in the regulation of arousal, anxiety, and emotions (Goddard et al., 2010; Lowry et al., 2005; McEwen, 2007; Ressler and Nemeroff, 2000). The critical areas in the locus ceruleus and raphe nuclei receive strong input from the amygdala (Retson and Van Bockstaele, 2013). These neuromodulators and anatomical regions also play critical roles in modulating breathing and sighing in particular (Pena and Ramirez, 2002; Viemari and Ramirez, 2006; Viemari et al., 2011), and they also regulate anxiety states (Lowry et al., 2005). However, it must be emphasized that neuromodulation is highly complex and the effect on all these behaviors is dependent on the affected receptor subtypes, second messenger systems as well as the modulatory state of the animals. Thus, very detailed information is needed to understand exactly how and under what conditions these aminergic and also peptidergic neuromodulators orchestrate and contribute to the link between breathing and emotion. In the case of many neuromodulators, we still do not know how they influence each other and how they affect the generation of sighs.

12 CONCLUSIONS

The focus of this review is on the close association between the neurobiology, physiology, psychology, and pathology of the sigh. Although it was impossible to consider in sufficient depth many of the important aspects related to this fascinating topic, it is still possible to arrive at several important take-home messages. Breathing, in general, and sighs, in particular, have not only important ventilatory functions but also equally important intrinsic roles within the central nervous system. The sigh plays a role in monitoring brain state changes, controlling arousal, and homeostatically regulating breathing variability. These functions are critical for day-to-day activities. When we speak, exercise, or sleep, breathing requires continued flexibility and adaptability, and the sigh seems to be critical in maintaining a healthy stability. In stressful, threatening, and challenging situations, sighs become essential for staging a flight-and-fight response. But the dual roles in regulating breathing variability and staging a flight-and-fight response can become pathological. Too little sighing and hypoarousal can lead to SIDS, too much sighing and hyperarousal can lead to panic disorders. Understanding how a healthy balance turns into pathologies is a fascinating problem that is clearly understudied. This review raises many open questions. We hope that it will inspire future research aimed at better understanding how breathing and sighing controls not only our physiological but also our emotional health, so that one day we as scientists will be able to catch up with the great artists who have long appreciated the important role of the sigh in regulating our emotions.

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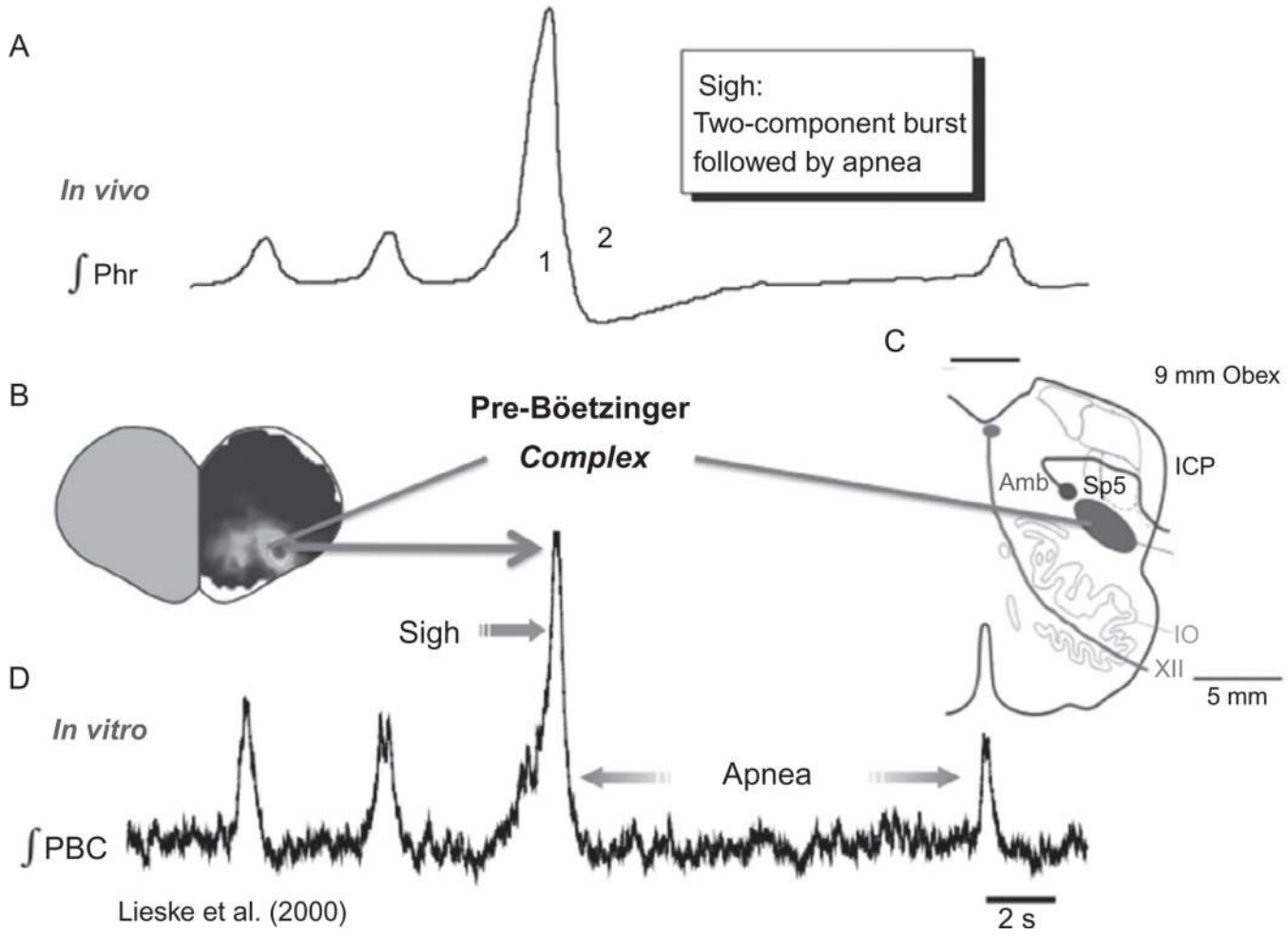

Figure 1.

The neuronal, anatomical, and physiological characteristics of the sigh and the pre-Bötzinger complex in an intact animal, in a human, and in an *in vitro* preparation. The sigh recorded as integrated phrenic nerve activity from an intact animal (A) and as integrated population activity (D) within the pre-Bötzinger complex (B and C), isolated in a transverse slice from the ventrolateral medulla of a mouse (B). (A) The sigh is characterized by a large inspiratory burst of activity (A1) that is triggered from a normal eupneic breath and that is followed by an apnea (A2) alsoreferred to as "postsigh apnea." (B) Rhythmically active transverse slice: the right side of the slice depicts an activity map of inspiratory activity. In this activity map, red represents the location of maximal integrated neuronal inspiratory activity generated during the sigh, which overlaps with the site of the pre-Bötzinger complex. (C) The pre-Bötzinger complexin a human. Note the close proximity to the Nucleus ambiguous (NA), which contains cardiac vagal neurons that are responsible for the generation of parasympathetic activity in the heart. The close proximity of NA and the pre-Bötzinger complex presumably plays a role in the cardiorespiratory coupling. (D) Integrated population activity recorded from the pre-Bötzinger complex. Note that the large-amplitude burst is followed by a period of apnea. (For interpretation of the references to color in this figure legend, the reader is referred to the online version of this chapter.)

Modified from (B) Lieske et al. (2000), (C) Schwarzacher et al. (2010), and (D) Lieske et al. (2000).

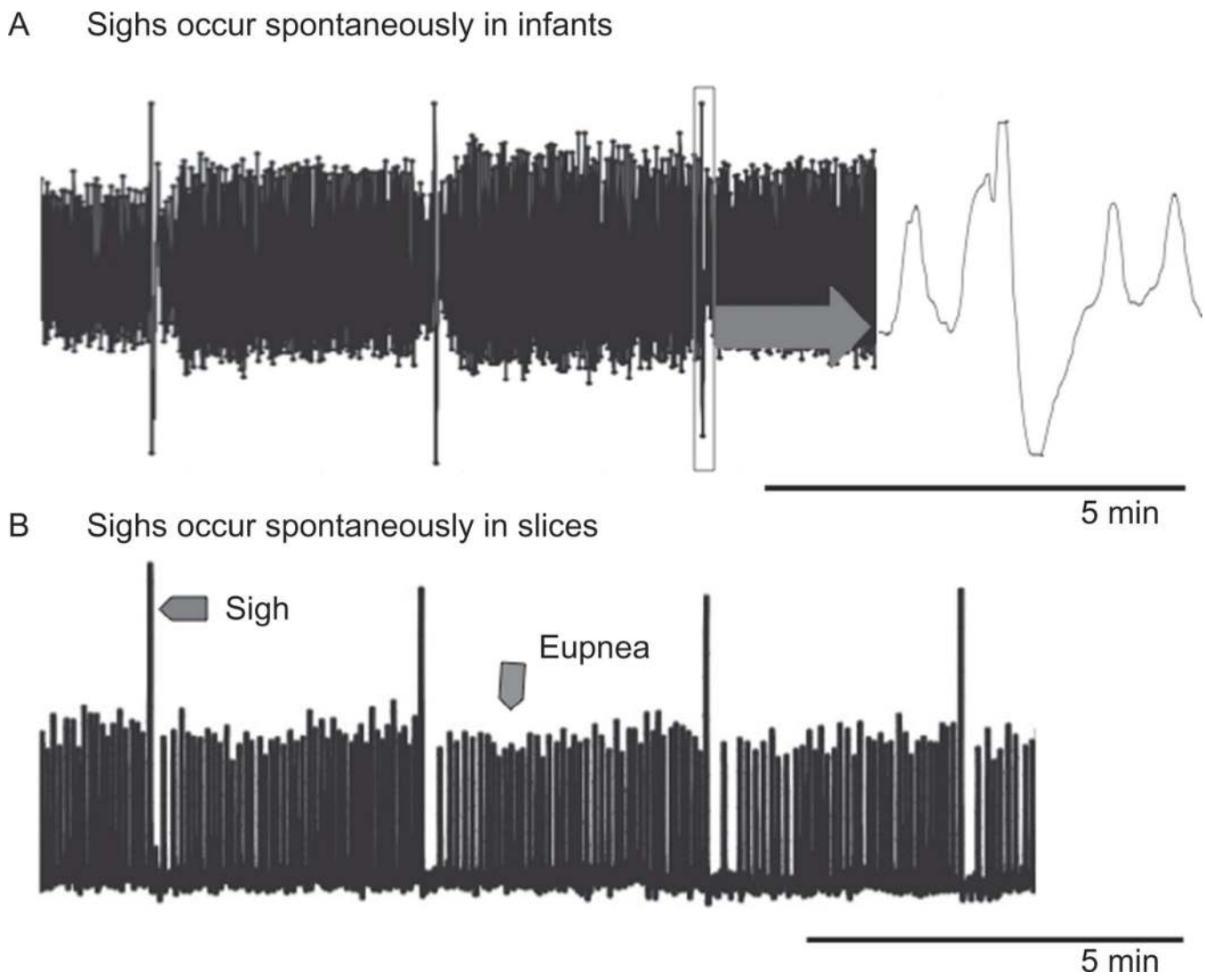

Figure 2.

Sighs occur spontaneously in humans. In addition, the neuronal activity critical for the generation of the sigh can be recorded as a "fictive sigh" when the underlying network is isolated in a brainstem slice preparation from a mouse. (A) Sighs are recorded as large-amplitude breathing movements using inductance plethysmography bands in a young infant. Note the regular occurrence of the large deflections that represent sighs. Inset marked by a red arrow: Each sigh consists of a large-amplitude inspiratory effort that is triggered by a eupneic breath and is followed by a short period of apnea. (B) Fictive sighs occur also spontaneously in the pre-Bötzinger complex isolated in slices obtained from neonatal mice. Note that the recordings in the human infant (A) and isolated slice (B) have the same time scale, illustrating the remarkable regularity of the sigh rhythmic activity, which occurs at a much slower time scale than the eupneic activity. (For interpretation of the references to color in this figure legend, the reader is referred to the online version of this chapter.)

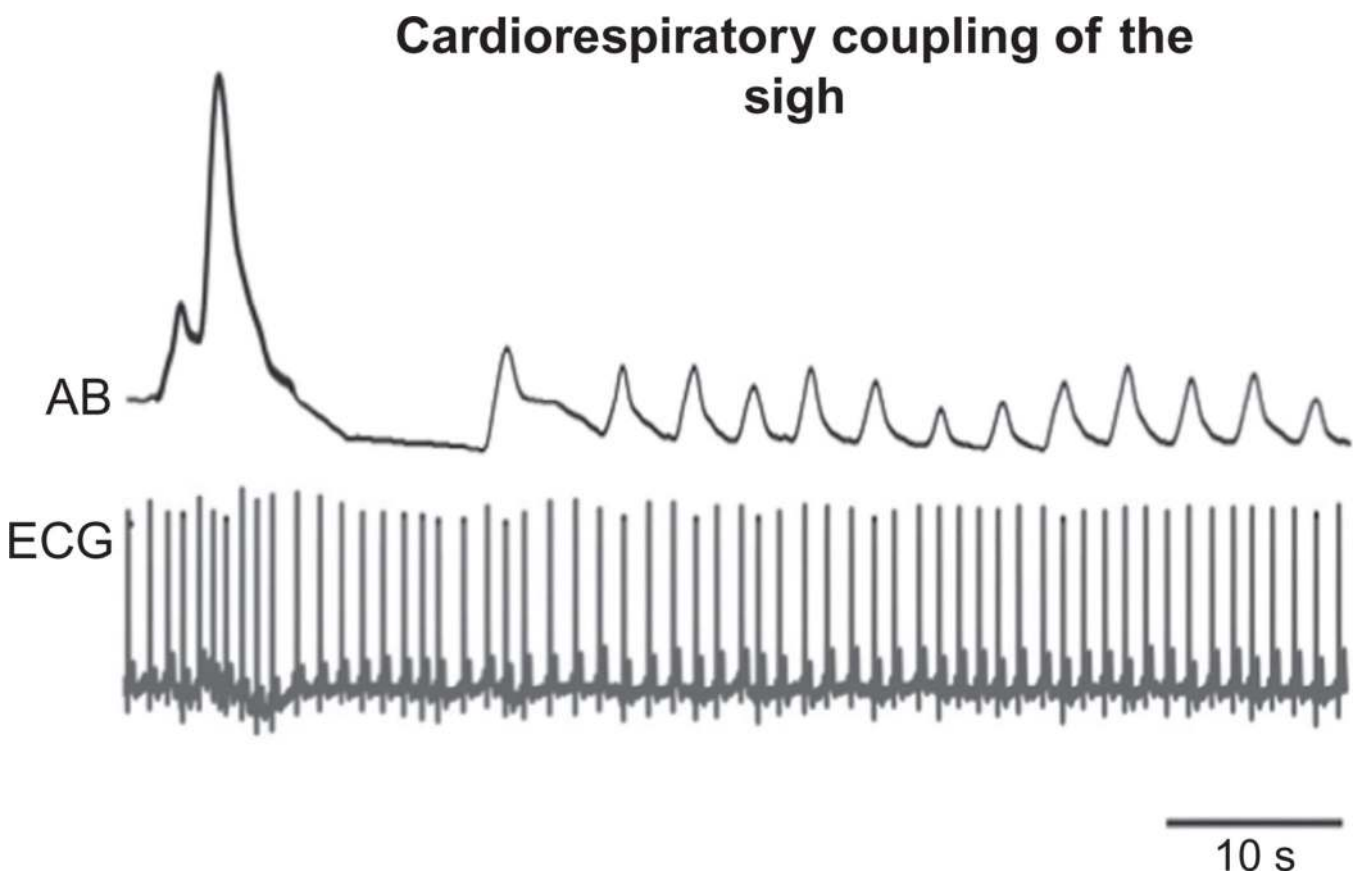

Figure 3.

Cardiorespiratory coupling of a sigh recorded in a healthy human subject. The sigh recorded with an inductance plethysmography brand from the abdomen (upper trace) is characterized by a heart rate increase followed by a heart rate decrease shown here in the simultaneously recorded electrocardiogram (lower trace). (For the color version of this figure, the reader is referred to the online version of this chapter.)

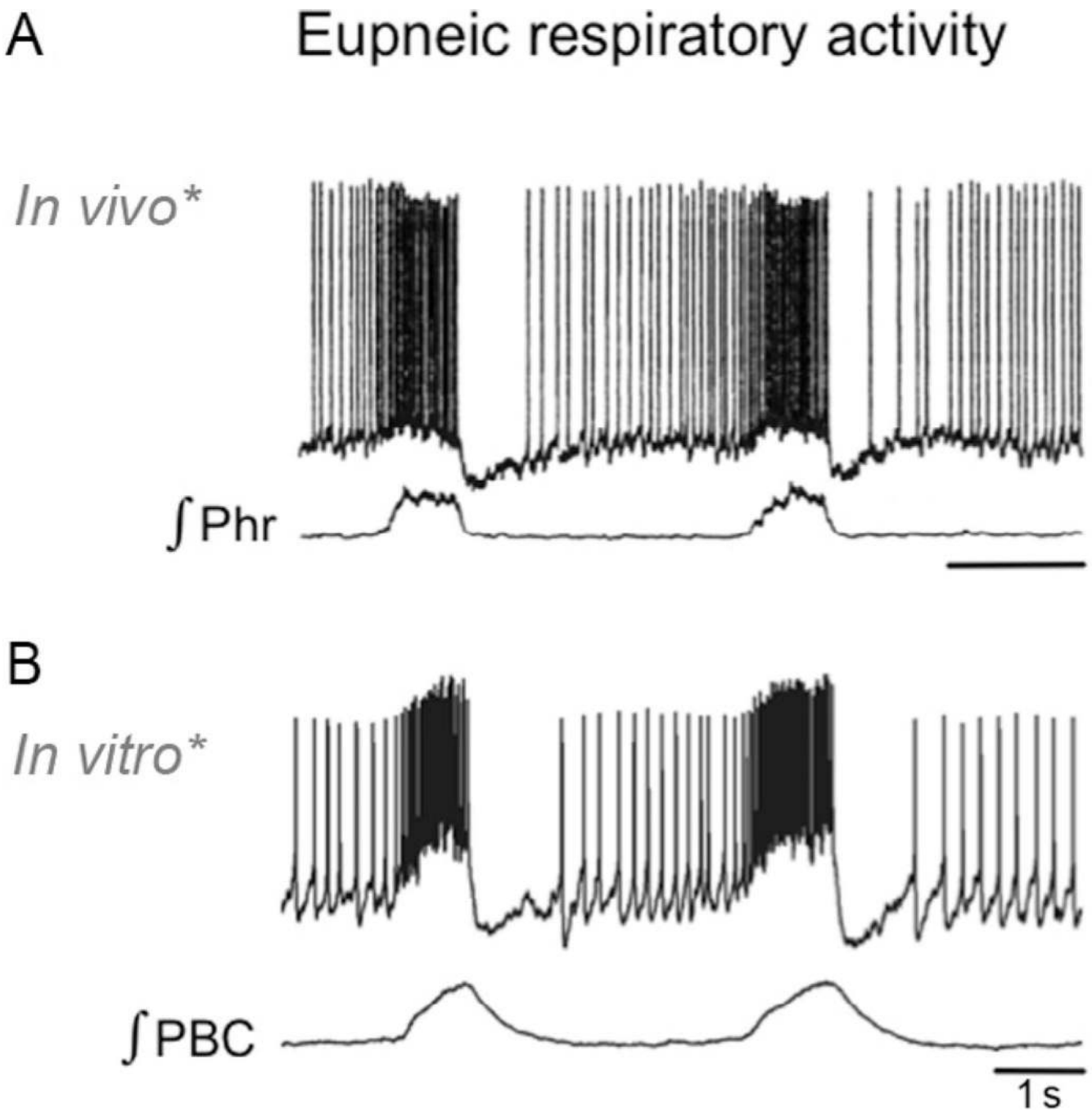

Figure 4.

Eupneic activity recorded from an intact animal and as a neuronal signal representing fictive eupneic activity in a transverse slice preparation. (A and B) Simultaneous intracellular recording from an inspiratory neuron within the pre-Bötzinger complex (upper trace) and integrated extracellularly recorded phrenic nerve activity (lower trace). (B) Simultaneous intracellular recording from an inspiratory neuron within the pre-Bötzinger complex (upper trace) and integrated extracellular population activity recorded of the pre-Bötzinger complex (lower trace). Note the remarkable similarities in the intracellularly recorded discharge

pattern of the inspiratory neuron both *in vivo* (A) and *in vitro* (B). (For the color version of this figure, the reader is referred to the online version of this chapter.)

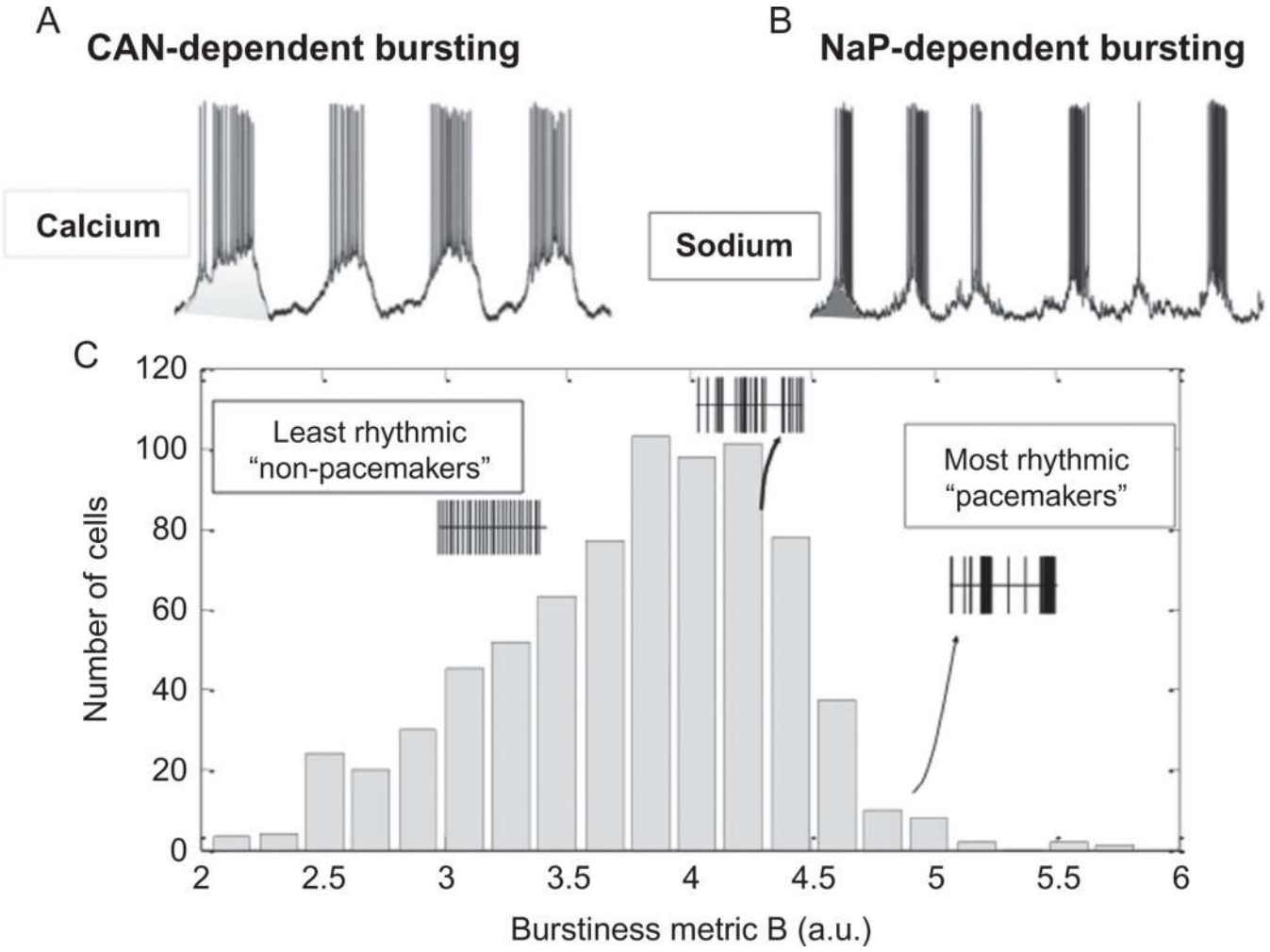

Figure 5.

Pacemaker activity recorded within the pre-Bötzinger complex. (A) Intracellular recording of a synaptically isolated pacemaker neuron in which bursting depends on the activation of the CAN current. (B) Intracellular recording of a synaptically isolated pacemaker neuron in which bursting is driven by the persistent sodium current. (C) The discharge pattern of respiratory neurons within the pre-Bötzinger complex follows a gradient. Some neurons are more bursting (right side) than others. Many neurons are weakly bursting and some are tonically active. This gradient illustrates that pacemaker neurons form not a discrete population. (For the color version of this figure, the reader is referred to the online version of this chapter.)

Modified from (A and B) Pena et al. (2004) and (C) Carroll and Ramirez (2013).

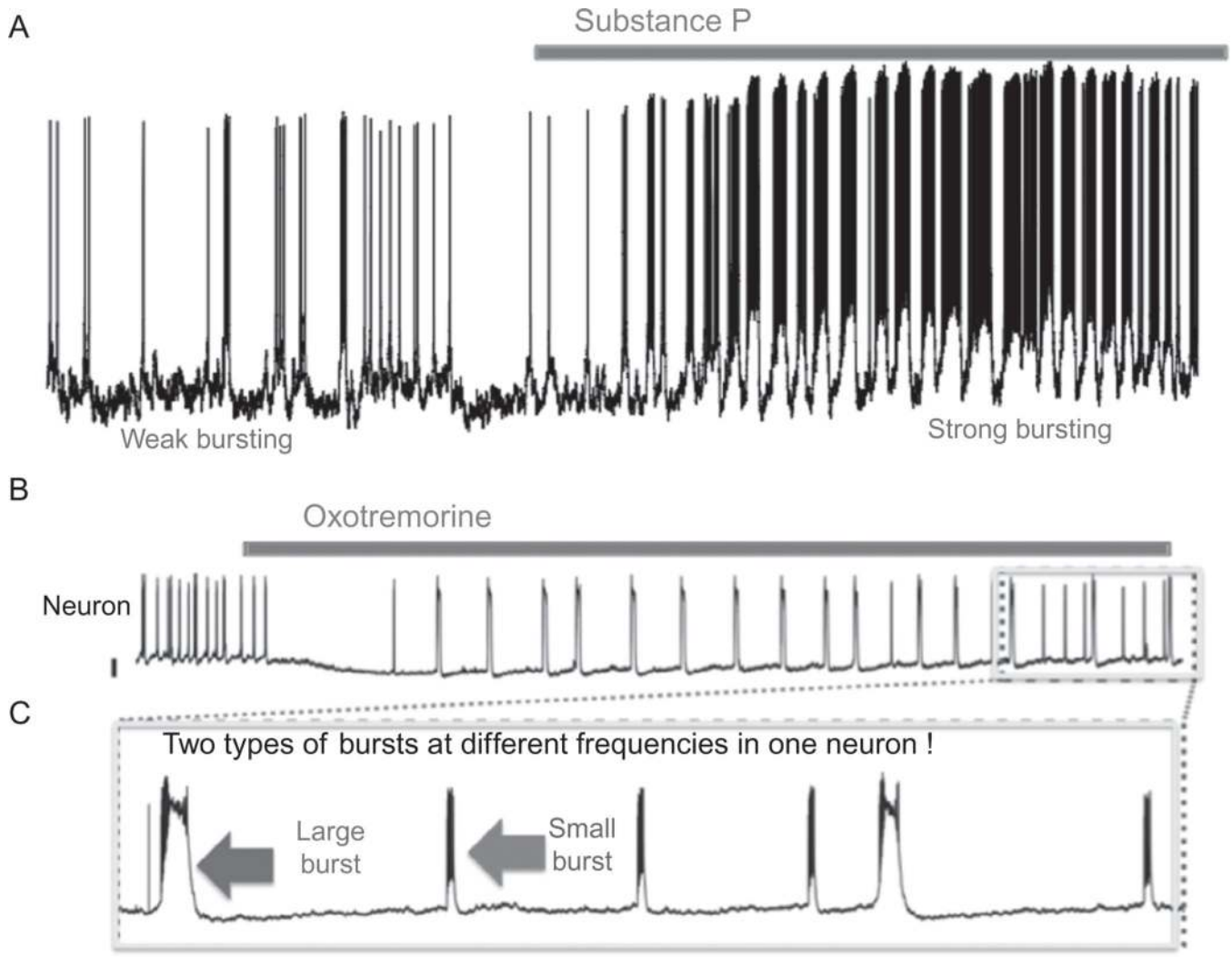

Figure 6.

Role of neuromodulators in determining the bursting characteristics of respiratory neurons. (A) Substance P turns a weakly burstingneuron into a strongly bursting pacemaker neuron. (B) Oxotremorine, an acetylcholine agonist, inhibits bursting in an INap-dependent pacemaker (see hyperpolarization) and induces the generation of a large-amplitude burst. As the modulatory effect weakens, small and large bursts overlap. (For the color version of this figure, the reader is referred to the online version of this chapter.)

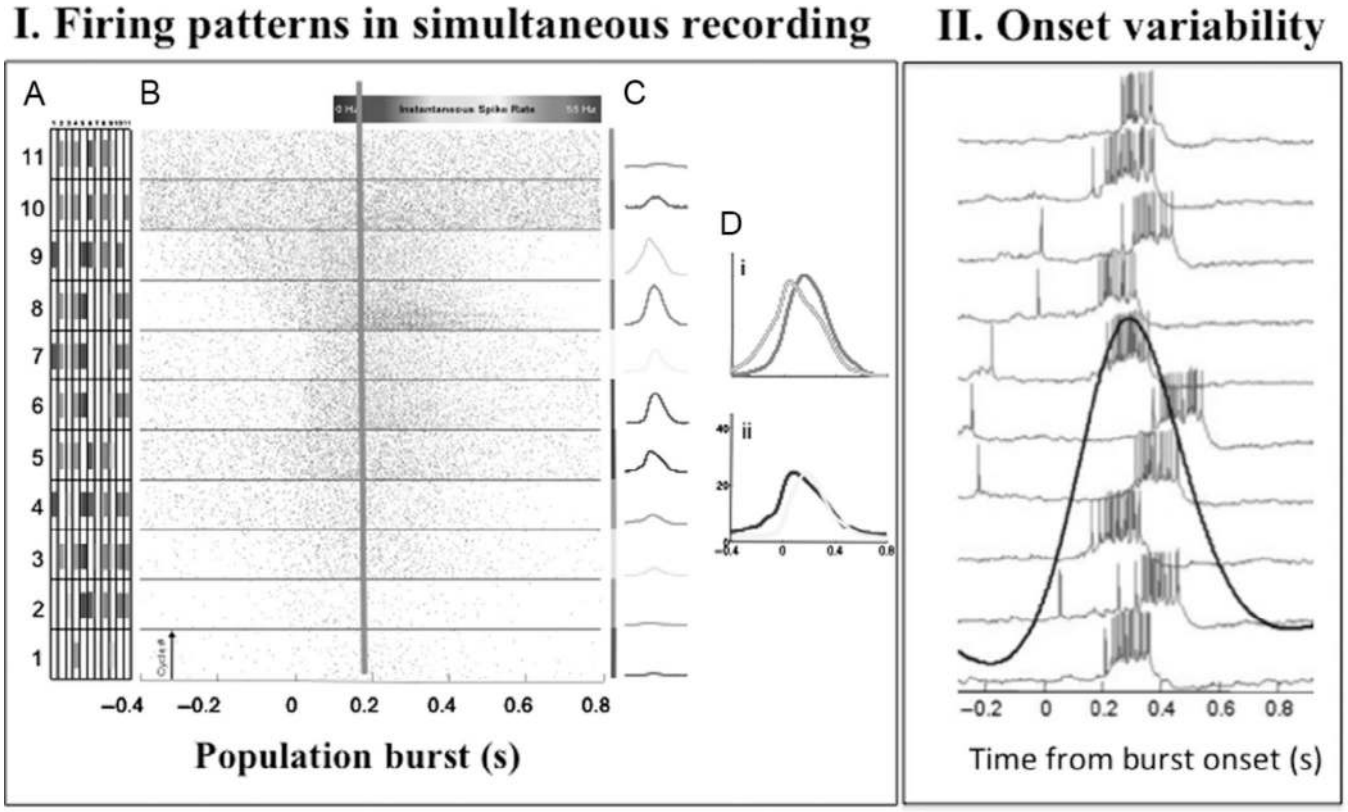

Figure 7.

The respiratory network in the pre-Bötzinger complex shows a gradient of discharge pattern as illustrated in the multiarray electrode recording (I). (I) The simultaneous multiarray recording from 11 neurons (see ordinate 1–11 in A) represents the cycle-by-cycle spiking behavior for each neuron within a respiratory cycle. Each block in A shows the spike time of a different neuron relative to the onset of inspiratory activity. In addition, the instantaneous spike rates are coded as a heat map from 0 to 55 Hz. C represents the average discharge for each neuron, and in D, the overlay of two pairs of averaged discharge activity shows that neurons have slightly different activation patterns. (II) The onset of discharge relative to the population activity is very variable as shown here for an intracellularly recorded pacemaker neuron. (For the color version of this figure, the reader is referred to the online version of this chapter.)

Modified from Carroll et al. (2013).

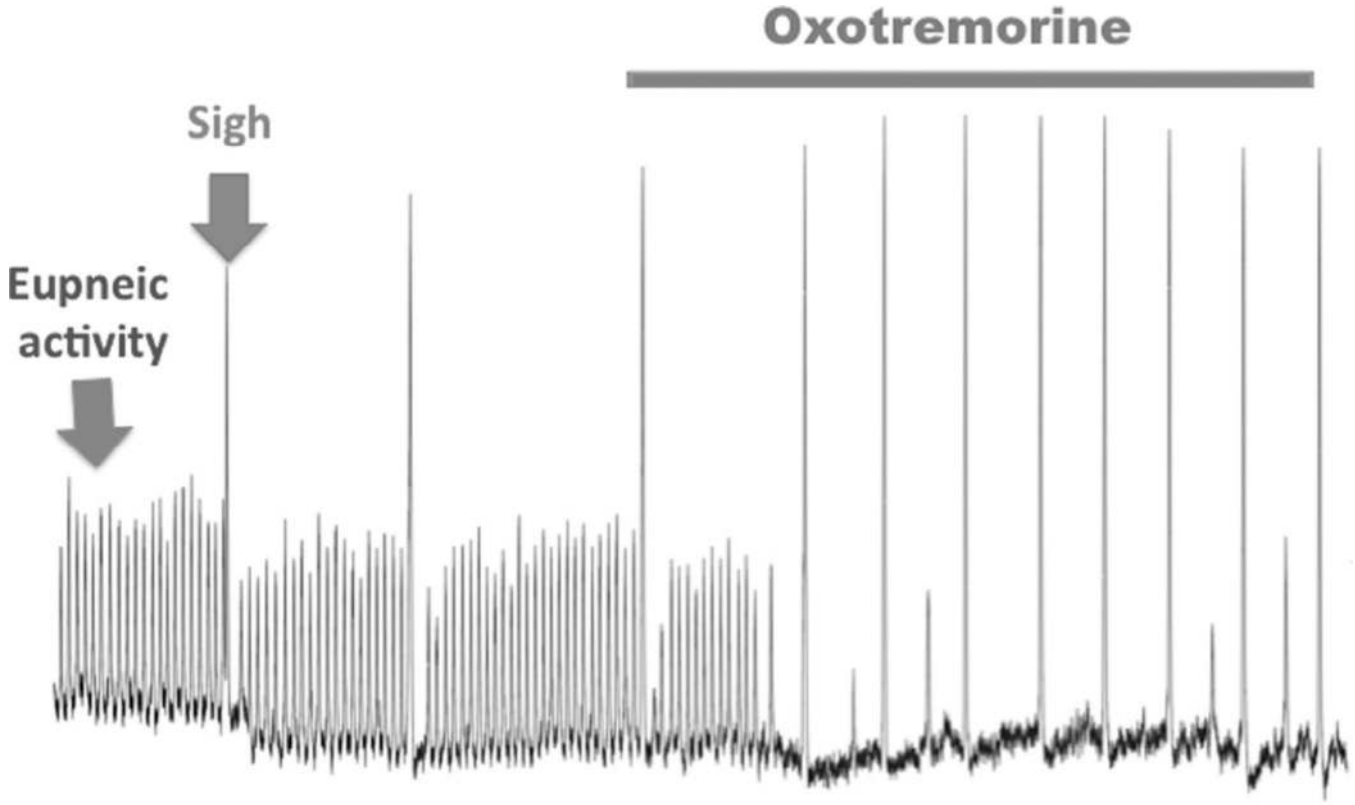

Figure 8.

Neuromodulators can differentially modulate eupneic and sigh activity, characterized as network activity in a functional brainstem slice preparation. The acetylcholine agonist oxotremorine specifically inhibits eupneic activity and activates sigh activity in the isolated pre-Bötzinger complex. (For the color version of this figure, the reader is referred to the online version of this chapter.)

Modified from Tryba et al. (2008).

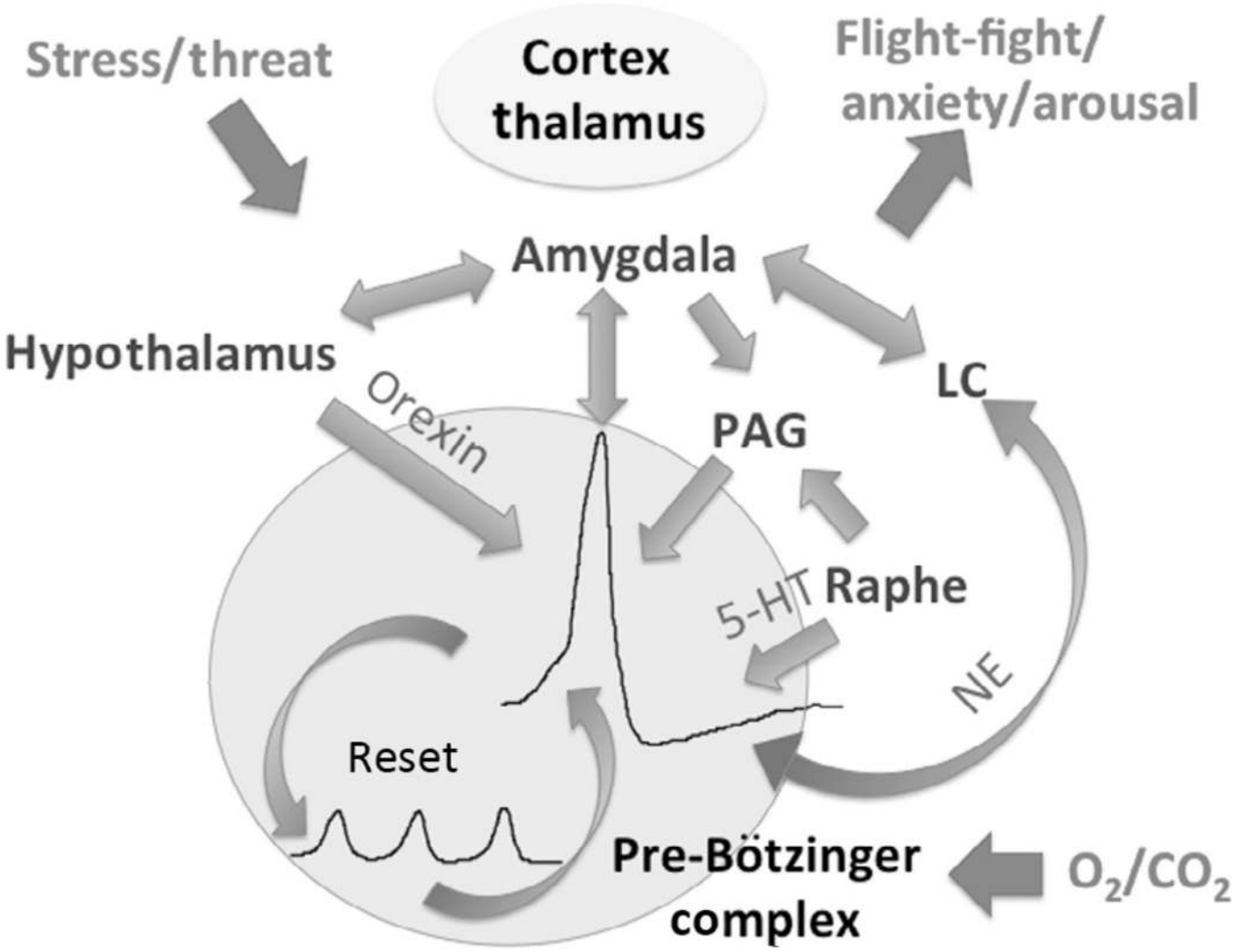

Figure 9.

The sigh has important roles in the control of arousal and in resetting breathing variability. The schematic represents some of the network interactions involved in centrally linking the sigh with areas such as the hypothalamus, amygdala, the locus ceruleus (LC), periaqueductal grey (PAG), and the Raphe nucleus involved in the control of the flight-fight response. The cortex and thalamus interact with these areas in a complex manner; the details are not depicted in this illustration for reasons of simplicity, but the reader is referred to the text for more details. Many of the interactions are reciprocal and function via the release of neuromodulators such as orexin, serotonin (5-HT), and norepinephrine (NE) acting on different receptor subtypes. (For the color version of this figure, the reader is referred to the online version of this chapter.)