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Breathing Rhythm and Pattern and Their Influence on Emotion

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Abstract

Breathing is a vital rhythmic motor behavior with a surprisingly broad influence on the brain and body. The apparent simplicity of breathing belies a complex neural control system, the breathing central pattern generator (bCPG), that exhibits diverse operational modes to regulate gas exchange and coordinate breathing with an array of behaviors. In this review, we focus on selected advances in our understanding of the bCPG. At the core of the bCPG is the preBötzinger complex (preBötC), which drives inspiratory rhythm via an unexpectedly sophisticated emergent mechanism. Synchronization dynamics underlying preBötC rhythmogenesis imbue the system with robustness and lability. These dynamics are modulated by inputs from throughout the brain and generate rhythmic, patterned activity that is widely distributed. The connectivity and an emerging literature support a link between breathing, emotion, and cognition that is becoming experimentally tractable. These advances bring great potential for elucidating function and dysfunction in breathing and other mammalian neural circuits.

Keywords

motor systems; central pattern generators; preBötzinger complex; synchrony; network dynamics; emotion

INTRODUCTION

Breathing is an astonishing behavior. Left to its own devices, breathing supports life by continuously driving gas exchange with incredible efficiency for up to a billion breaths in a human life span. Breathing is controlled by the nervous system, and given the rhythmicity of ventilation, we are primed to think that the underlying mechanisms are straightforward, even trivial, especially compared to behaviors that require learning and memory, sensory

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processing, fine motor control, decision-making, and other higher cognitive functions. Control of breathing is often thought to be akin to control of the heart, its partner in moving blood gases. Yet the heart has one job, to pump blood using cardiac and smooth muscle, which relegates the nervous system to a modulatory role. In contrast, the breathing central pattern generator (bCPG) generates and transmits rhythmic, patterned activity to skeletal muscle that adjusts each breath to (*a*) ensure adequate O_2 supply and acute CO_2 removal in the face of changing metabolic demands and environmental conditions, (*b*) protect airway patency and lung health, and (*c*) participate in and coordinate with other behaviors (Figure 1a). Breathing must be exceptionally robust and labile to accomplish all this, an incredible challenge well met by evolution, with the result being a complex behavior with surprising facets that go beyond producing airflow.

Almost every behavior or state and a vast array of endogenous neurochemicals such as amino acids, biogenic amines, and a large number of neuropeptides regulate or affect breathing (Figure 1a). Exogenous drugs like opioids and anesthetics have potent, even fatal, effects. Many diseases better known for affecting cognition also affect the bCPG (Figure 1a). Moreover, breathing rhythms are detected throughout the nervous system where they have no apparent role in ventilation, for example, respiratory modulation of the pupil (Borgdorff 1975) or fear response (Zelano et al. 2016). Breathing practice, that is, short-term or extended repeated changes in breathing pattern, can profoundly, and usually positively, modulate emotion and cognition (Lavretsky & Feldman 2021, Weng et al. 2021). With that in mind, we encourage the reader to take a few deep breaths before proceeding.

A number of recent reviews cover a variety of important topics in the control of breathing (Supplemental Appendix, Note 2). We focus our review on selected recent advances in our understanding of the bCPG, including inspiratory rhythm generation, active expiration, and breathing as a modulator of emotion and cognition.

BREATHING RHYTHM AND PATTERN

Inspiratory Rhythm

In 1990, the preBötzinger complex (preBötC) (Figure 1b), a bilateral structure in the ventrolateral medulla with approximately 3,000 neurons in rodents and around 10,000 in humans, was hypothesized as the engine for inspiratory rhythm (Feldman et al. 1990, Smith et al. 1991, Schwarzacher et al. 2011); now, after hundreds of papers and reviews, the evidence in support of the preBötC as the kernel for breathing is overwhelming. Because the most salient feature of breathing is its relentless and essential rhythmicity, delineating preBötC rhythmogenic mechanisms is a fundamental quest.

The initial discovery of the preBötC included observations of neurons with bursting-pacemaker properties in vitro (Smith et al. 1991). Intrinsic conductances help generate, maintain, and terminate bursts, but a pacemaker neuron hypothesis that places these currents together in special excitatory neurons, akin to cardiac pacemaker cells, that collectively drive inspiratory rhythm, remains contentious. While a rhythm driven by pacemaker neurons is compelling, considerable data in vitro establish that they are not necessary for rhythmogenesis (Del Negro et al. 2018), with no evidence of their presence in vivo.

Another usual suspect thought to be essential for rhythmogenesis is synaptic inhibition, where activity built up during inspiration crosses a threshold that activates a powerful feedback inhibition to terminate the burst and is followed by a refractory period before the next cycle begins (von Euler 1983, Feldman 1986, Smith et al. 2007, Ausborn et al. 2018). The inhibition hypothesis also fails critical tests (Janczewski et al. 2013). Therefore, we view with considerable skepticism research built on the premise that either or both of these factors constitute essential mechanisms for rhythmogenesis. Because no recent data provide a compelling reason to reconsider these issues, we refer readers to our previous reviews (Feldman & Del Negro 2006, Feldman et al. 2013, Del Negro et al. 2018). Instead, we suggest that inspiratory rhythmogenesis is an emergent property of the preBötC network.

Burstlets

A long-standing view of rhythmogenesis underlying periodic movements is that production of large-amplitude population bursts is necessary. The neural substrate of burst-dependent inspiratory rhythmogenesis is thought to be Developing Brain Homeobox Protein 1 (Dbx1)-derived type 1 preBötC inspiratory neurons (Rekling et al. 1996; Gray et al. 1999, 2010; Bouvier et al. 2010), whose intrinsic membrane properties facilitate large-magnitude bursts during inspiration. Somewhat overlooked were low levels of slowly incrementing ensemble activity preceding inspiratory bursts, that is, during preinspiration, that we now propose are a latent signature of an emergent mechanism for rhythmogenesis (Figure 2). In vitro, when excitability is high, inspiratory bursts occur in every preBötC cycle driving motor output, typically monitored via discharge of the hypoglossal nerve (XIIn), which innervates the tongue. However, when excitability is lowered, XIIn bursts often do not appear at expected times, yet, within the preBötC, rhythmic bouts of synchronous low-level population activity, called burstlets, appear (Figure 2a). The missed XIIn bursts result from the failure of burstlets to trigger preBötC bursts that would propagate to XII motoneurons. In the appropriate conditions, the preBötC rhythm consists solely of burstlets, with no bursts in sight and where individual neurons periodically fire low-frequency action potentials (Figure 2b). As burstlet activity resembles the preinspiratory activity preceding bursts on both the population and single-neuron level (Figure 2c), we hypothesize that the rhythmogenic signature is the burstlet, not the burst (Kam et al. 2013a, Feldman & Kam 2015, Kallurkar et al. 2020). Significantly, burstlets can be induced to appear in vivo in the diaphragmatic electromyogram, that is, inspiratory motor output, by increasing preBötC excitability in anesthetized, vagotomized rats (Kam et al. 2013a) (Figure 2a), revealing that burstlets are not merely an in vitro epiphenomenon. We consolidated these observations in burstlet theory, where the key rhythmogenic element is the burstlet, which under normal conditions triggers with exceptionally high probability a burst that then propagates to inspiratory motoneurons. A strong prediction of this theory is that manipulations that alter burst rhythm should similarly alter burstlet rhythm. Opioids, powerful depressants of breathing rhythm, provided an ideal test (Sun et al. 2019).

preBötC and Opioids

The robust bCPG has a profound limitation, its intrinsic sensitivity to opioids, which underlies opioid-induced respiratory depression (OIRD) that is too often fatal (Wilson et al. 2020). While opioids can act at sites throughout the nervous system to impact

breathing (Palkovic et al. 2020), the near or complete apnea of severe OIRD appears to be (predominantly) mediated by μ-opioid receptors (μORs) in the preBötC and Kölliker-Fuse/parabrachial nucleus (KF/PBN), where local injections of naloxone, a potent μOR antagonist; genetic deletion of μORs; or chemogenetic activation of μOR neurons in the presence of opioid agonists reduces OIRD (Montandon et al. 2011, Levitt et al. 2015, Stucke et al. 2015, Sun et al. 2019, Bachmutsky et al. 2020, Saunders & Levitt 2020, Varga et al. 2020, Liu et al. 2021). Acknowledging that KF/PBN neurons contribute to OIRD in ways not yet fully understood, we focus here on the preBötC and illustrate how opioids may act to modulate breathing.

Elucidation of opioidergic effects in the preBötC primarily comes from studies in rodent medullary slices generating a breathing rhythm. Local microinjection of DAMGO, a μOR agonist, into the preBötC results in a dose-dependent gradual decrease in burst frequency (Johnson et al. 1996, Gray et al. 1999). Is this opioidergic effect on burst frequency mediated by effects on burstlets, as predicted by burstlet theory? It appears so, as DAMGO depresses both burst and burstlet rhythms (Sun et al. 2019) (Figure 2d,e).

To affect rhythmogenesis directly, opioids should target the preBötC subpopulations involved in generating or modulating rhythm. Indeed, Dbx1-derived type 1 preBötC neurons express μORs (*Oprm1*) (Hayes et al. 2017, Sun et al. 2019) and are hyperpolarized by DAMGO (Gray et al. 1999, Montandon et al. 2011). While μORs may be sparse in preBötC (~8% in adult mice), genetic deletion of μORs in Dbx1-derived neurons completely abrogates opioid-mediated depressant effects on inspiratory rhythm in medullary slices (Sun et al. 2019, Bachmutsky et al. 2020).

How do cell-intrinsic pre- and postsynaptic effects of opioids underlie their effects on preBötC rhythmogenesis? A μOR signaling pathway involving β-arrestin (Raehal et al. 2005) does not appear to play a role in OIRD (Gillis et al. 2020, Bachmutsky et al. 2021). Rather, reduced excitability via G protein–coupled inwardly rectifying K^+ (GIRK) channel activation (Gray et al. 1999, Montandon et al. 2016, Varga et al. 2020) and decreased synaptic release among μOR-expressing preBötC Dbx1-derived neurons appear to work together to reduce the probability that a critical number of neurons are simultaneously active in the postburst refractory period (Baertsch et al. 2021, Burgraff et al. 2021). These effects prolong the time required for preBötC neurons to synchronize and generate burstlets followed by bursts (Feldman & Kam 2015, Wei & Ramirez 2019, Ashhad & Feldman 2020).

Synchrony

If burstlets are the rhythmogenic engine, we need to rethink our current notions of the underlying mechanisms because rhythm emerges with considerably less neuronal depolarization than that required in conventional burstcentric pacemaker neuron- or inhibitory ring-based models (e.g., see Smith et al. 2007, Ausborn et al. 2018). The low levels of depolarization during burstlets and preinspiratory activity are inconsistent with rhythmogenic mechanisms based on regenerative inward currents, for example, calcium-activated nonspecific cation current and persistent sodium current (I_{NaP}) (Del Negro et al. 2002, Koizumi & Smith 2008, Yamanishi et al. 2018). Furthermore, preBötC pacemaker neuron–based models where burstlet-like activity emerges with increases in excitability

(Bacak et al. 2016) are belied by experiments (Kallurkar et al. 2020). We postulate instead that synchrony, an emergent network property, underlies burstlet-driven rhythms.

If excitatory drive into the preBötC is insufficient or inhibitory tone is too high, that is, the background excitation-inhibition (Exc-Inh) balance is low, then type 1 preBötC neurons in vitro fire asynchronously at a low frequency and there is no rhythm (Figure 3a). When background Exc-Inh balance is high enough to augment the efficacy of spike transmission, then asynchronous firing among type 1 preBötC neurons in vitro early in the cycle evolves into progressive synchronization of their discharge. Here, synchrony refers to correlated firing of neurons on a shorter than 50-ms timescale (Ratté et al. 2013), observed as the near instantaneous excitatory postsynaptic potential (EPSP) correlation between pairs of preBötC output (e.g., type 2) neurons (Figure 3c). Increasingly synchronized synaptic input produces higher rates of firing in these neurons in the late interburst(let) interval, leading to a burstlet or preinspiratory activity (Gray et al. 1999, Kam et al. 2013a, Cui et al. 2016, Sun et al. 2019, Ashhad & Feldman 2020) (Figure 3b, **subpanel *i***). The sequence of activation within the type 1 population is not deterministic, thus onset times and firing patterns differ from cycle to cycle (Carroll & Ramirez 2013, Ashhad & Feldman 2020). A reflection of this stochastic network assembly is the considerable variability in the preinspiratory period and respiratory cycle within and across experiments (Carroll & Ramirez 2013, Cui et al. 2016, Ashhad & Feldman 2020).

Whether a burstlet triggers a burst is an all-or-none process. Burstlets induce a burst if the spike-to-spike synchronization in the rhythmogenic population reaches a tipping point (Figure 3b, **subpanel *ii***) that is a function of the number, activity level, and connectivity of type 1 neurons (Ashhad & Feldman 2020, Slepukhin et al. 2020). Failure to reach the requisite level of synchrony, due to low levels of network excitability, high levels of inhibition (Shao & Feldman 1997, Gray et al. 1999, Sherman et al. 2015, Ashhad & Feldman 2020, Gómez et al. 2021), or perhaps activation of KCNQ channels that underlie M-type K^+ current (Wei & Ramirez 2019, Revill et al. 2021), results in burstlet termination, and the network returns to a desynchronized state (Slepukhin et al. 2020) (Figure 3b, **subpanel *i***). On the other hand, with the background Exc-Inh balance shifted sufficiently toward excitation, the ensemble activity of type 1 neurons reaches the tipping point, and coincident EPSPs recruit type 2 preBötC output neurons, including those expressing the somatostatin (SST) peptide (Tan et al. 2008, Cui et al. 2016), which amplifies network activity to generate an inspiratory burst (Kam et al. 2013a, Ashhad & Feldman 2020, Kallurkar et al. 2020). With the ensuing burst, the burstlet appears as preinspiratory activity (Figures 2b,c and 3b, **subpanel *ii***).

Once a burst is initiated, what factors determine its duration? First, inhibition can shorten burst duration, as when signals originating in pulmonary stretch receptors shorten inspiratory duration. Nevertheless, after pharmacological blockade of all major inhibitory synaptic receptors, preBötC bursts and burstlets continue to self-terminate in vitro (Feldman & Smith 1989, Brockhaus & Ballanyi 1998, Ashhad & Feldman 2020) and in vivo (Büsselberg et al. 2001a,b; Janczewski et al. 2013). Second, outward currents whose activation depends on the vigorous spiking associated with bursts, for example, electrogenic Na/K ATPase pump current, Na^+-dependent K^+ current, ATP-dependent K^+ current, and a KCNQ-mediated

M-type K^+ current, affect burst duration and termination (Del Negro et al. 2009, Krey et al. 2010, Gray & Johnston 2021, Revill et al. 2021). Third, short-term synaptic depression hastens burst termination (Guerrier et al. 2015, Kottick & Del Negro 2015). Fourth, inactivation of inward currents like I_{NaP}, which are active during bursts, contributes an additional burst-terminating outward current (Del Negro et al. 2002, Koizumi & Smith 2008, Yamanishi et al. 2018). And fifth, preBötC network desynchronization may also contribute (Ashhad & Feldman 2020, Slepukhin et al. 2020).

Emergent mechanisms depend on network properties such as connectivity. Data on such properties are largely lacking, with a wide range of preBötC degree of connectivity estimates and proposed network structures (Butera et al. 1999, Rekling et al. 2000, Hartelt et al. 2008, Carroll & Ramirez 2013). The most direct measurements, from paired whole-cell recordings, suggest an approximately 13% one-way connection probability (Rekling et al. 2000). What kind of microcircuits with this connectivity could produce burstlets and bursts? Models of randomly connected networks, where the strength of a small fraction of synapses far exceeds their mean, that is, synaptic strengths are lognormally distributed, provide the best fit (Buzsáki & Mizuseki 2014, Slepukhin et al. 2020). Synchronization in such networks emerges from random combinations of coincidently active (Kam et al. 2013b) type 1 neurons (Vogels et al. 2005, Faisal et al. 2008, Carroll & Ramirez 2013, Ashhad & Feldman 2020) and is consistent with variability in the preinspiratory period observed experimentally (Carroll & Ramirez 2013, Cui et al. 2016, Ashhad & Feldman 2020). This model network also reproduces experiments in which targeted stimulation of four to nine preBötC neurons evokes, with considerable temporal dispersion, XIIn motor output (Kam et al. 2013b) (Figure 2c).

Such emergent network-dependent rhythmogenesis imbues the system with robustness and lability, properties that are a signature of attractor dynamics, that is, the tendency of a network to evolve toward a fixed activity state regardless of its starting point (Diesmann et al. 1999, Vogels et al. 2005, Ermentrout et al. 2008, Kumar et al. 2010, Knierim & Zhang 2012). Robustness comes from the presence of a tipping point that further synchronizes the network and ensures a burst that propagates to motoneurons to generate airflow. The lability comes from the numerous possible routes through which network activity reaches the tipping point, as well as dynamic regulation of the tipping point by neuromodulators and the background Exc-Inh balance (Janczewski & Feldman 2006, Janczewski et al. 2013, Kam et al. 2013a, Baertsch et al. 2018) (Figure 3). Thus, the synchronization dynamics of the preBötC contributes significantly to the resilience of breathing while keeping the behavior labile. Flexible preBötC dynamics are advantageous in many ways, enabling (*a*) rapid changes in phase durations, amplitudes, and breathing frequency with consequent quick changes in ventilation; (*b*) a variety of breathing patterns such as sighs, gasps, coughs, and gags; and (*c*) integration with other behaviors (Figure 1a) like swallowing, chewing, phonation, and locomotion.

When the balance between robustness and lability is disturbed, breathing may become unstable, that is, fail to maintain blood gas homeostasis, and conditions such as hypoxemia or hypercapnia result (Jubran et al. 1997). Stability and variability in breathing are often confounded. Ventilatory instability can occur at the extremes of respiratory rate, when

breathing is very slow or very fast, or render breathing more susceptible to perturbations, as in central sleep apnea (Orr et al. 2021) or OIRD (Palkovic et al. 2020). In contrast, there is little to no evidence that eupneic respiratory variability, measured by the variance in cycle-by-cycle duration and/or tidal volume, is inherently detrimental to health. Indeed, variability is quite typical of breathing across a variety of states (Donaldson 1992, Fiamma et al. 2007, Kabir et al. 2010) and, like heart rate variability, may even be a signature for healthy breathing (Glass 2001, Samara et al. 2009, Hess et al. 2013). Experimental manipulations that change preBötC excitability, including increased chemosensory drive, changes in extracellular K^+ concentration, and alterations in inhibitory and excitatory afferent signals, can all affect respiratory variability, perhaps via changing the network interactions operating on the fast timescale of neuronal synchronization (milliseconds) and the slower recovery from the postburst refractoriness (more than tens of milliseconds) (Del Negro et al. 2009, Doi & Ramirez 2010, Crone et al. 2012, Kam et al. 2013a, Sun et al. 2019).

Inspiratory Patterning and Synchrony Propagation

Quasi-independent control of breathing frequency and pattern has long been recognized (Clark & von Euler 1972, Feldman 1986), where the rate and depth of inspiratory and expiratory airflow may be decoupled from the duration of inspiratory and expiratory phases. In rodents, both in vivo and in slices, substantial changes in frequency can be induced with little change in inspiratory burst amplitude and duration; conversely, changes in inspiratory burst shape can be induced with little change in frequency. Burstlet theory suggests that rhythm and pattern generation can be functionally separated even within the preBötC itself with further elaboration of pattern by structures outside the preBötC. How then does inspiratory rhythm transform into a motor pattern?

Bursts from preBötC output neurons propagate through discrete populations of inspiratory premotor and motoneurons to activate muscles for inspiration (Figure 1a). Short-timescale correlations, that is, synchronization, in neuronal spiking in vivo (Funk & Parkis 2002, Mellen et al. 2003, Parkis et al. 2003) and inspiratory-modulated high-frequency oscillations with peak frequencies between 50 and 120 Hz (Bruce 1988, Chritaakos et al. 1988, Kocsis & Gyimesi-Pelczer 1997) are seen throughout the bCPG (Cohen 1973, Cohen et al. 1974, Cohen & Feldman 1984, Chritaakos et al. 1988). This finding suggests a propagation mechanism involving preBötC synchrony, where the correlated firing of preBötC output neurons (Figure 3c) assures highly reliable, essentially lossless, transmission of inspiratory bursts to inspiratory muscles more efficiently and reliably compared to mechanisms that rely solely on an unfluctuating firing rate (Parkis et al. 2003, Kremkow et al. 2010, Kumar et al. 2010, Ratté et al. 2013; see also Mainen & Sejnowski 1995, Ermentrout et al. 2008).

BEYOND INSPIRATION

In addition to inspiratory motor outflow through premotoneurons and motoneurons, the bCPG includes a column of breathing-related nuclei along the ventral medulla that interact with the preBötC to generate other respiratory phases during normal breathing, particularly when not at rest (Alheid & McCrimmon 2008, McCrimmon et al. 2008) (Figure 1). These

and other brainstem regions project directly to and receive projections from both excitatory and inhibitory preBötC neurons, representing recurrent circuits for modulation of breathing (Yang & Feldman 2018, Yang et al. 2020) (Figure 1b). Below, we discuss structures mediating expiratory rhythm and postinspiration, respiratory-related inhibitory structures, and regions providing afferent modulation to the bCPG.

Expiratory Rhythm

With greater demand for O_2 or significant elevation in CO_2 above rest, expiration transforms from passive to active by recruitment of internal intercostal and abdominal muscles. Contraction of these expiratory muscles moves more air more quickly out of the lungs, so the next inspiration starts at a lower lung volume allowing for larger breaths at shorter intervals—in other words, ventilation increases. Active expiration requires microcircuits outside the preBötC. A conditional oscillator (Mellen et al. 2003, Janczewski & Feldman 2006, Magalhães et al. 2021), the lateral parafacial (pF_L), is postulated to generate expiratory rhythm, but it is normally inhibited at rest (Pagliardini et al. 2011, Flor et al. 2020) (Supplemental Appendix, Note 3).

What factors evoke active expiration? Hypercapnia, an increase in CO_2, disinhibits the pF_L to evoke active expiration (Pagliardini et al. 2011, Huckstepp et al. 2015, de Britto & Moraes 2017, Flor et al. 2020). In addition, pF_L rhythmicity may be driven by (*a*) pF_V chemosensors directly and via links that include the Kölliker-Fuse nucleus (Jenkin et al. 2017, Barnett et al. 2018), (*b*) sympathetic C1 neurons sensing hypoxia that project directly to the pF_L (Malheiros-Lima et al. 2020), and (*c*) neuron-glia interactions that augment but do not directly evoke active expiration (Huckstepp et al. 2016).

Active expiration is useful apart from increasing ventilation. In contrast to the preBötC, the pF_L is insensitive to opioids (Takeda et al. 2001, Mellen et al. 2003), and, in neonatal and juvenile rodents, opioid agonists silence the preBötC, but due to active expiratory rhythm, expiratory motor output continues (Jacquin et al. 1996, Janczewski & Feldman 2006). This differential sensitivity may play a role in neonatal resistance to the breathing-depressant effects of elevated maternal endogenous opioids at birth (Jansen & Chernick 1983). Additionally, active expiration wards off apneas, which is helpful during sleep (Boutin et al. 2017).

Are There Other Breathing Oscillators?

While airflow has two distinct phases during eupneic breathing in mammals, inhale and exhale, the underlying muscle activity often, but not always, exhibits three discrete phases. When present, the third phase, postinspiration, occurs right after the peak of inspiration when eccentric diaphragm contraction and airway muscle constriction reduce recoil-driven expiratory airflow; this improves gas exchange by slowing the reduction in lung volume.

A long-standing controversy is whether postinspiration is a distinct obligatory phase required for the normal breathing cycle or an elaboration of a motor pattern for coordination with nonventilatory behaviors. We argue that since normal breathing does not always have a postinspiratory phase, such activity is not essential for generating breathing rhythm (Feldman & Del Negro 2006, Feldman et al. 2013, Del Negro et al. 2018). Regardless, when

postinspiration is present, does it originate in a distinct oscillator coupled to the preBötC and pF_L?

The KF can modulate the activity of muscles that affect postinspiratory airflow and participate in generation of postinspiratory behaviors such as vocalization and swallowing (Orem & Trotter 1992, Dutschmann & Herbert 2006, Dutschmann & Dick 2012, Poon & Song 2014). Such postinspiratory behaviors are shaped by the KF in response to its afferent projections from the nucleus of the solitary tract (NTS), pF_V, and amygdala. There is no evidence that KF can act as a postinspiratory oscillator.

In neonatal mouse horizontal slice preparations in vitro, a cluster of glutamatergic-cholinergic neurons medial and caudal to the facial nucleus (Lima et al. 2019, Nasirova et al. 2020) is conditionally rhythmic during postinspiration (Anderson et al. 2016). This cluster, dubbed the postinspiratory complex (PiCo), is postulated to comprise a dedicated postinspiratory rhythm generator obligatory for normal breathing (Anderson et al. 2016). However, a number of experiments contradict this hypothesis. Inhibiting PiCo in vivo reduces but does not abolish postinspiratory vagal nerve activity (Anderson et al. 2016), suggesting that postinspiration relies on sites other than PiCo. Furthermore, the glutamatergic-cholinergic neurons explicitly defined as PiCo have not been corroborated as obligatory for breathing-related postinspiration. In intact rats, the presumptive same set of glutamatergic-cholinergic neurons act as relays for swallowing and may even be part of the swallowing central pattern generator (CPG) (Toor et al. 2019). Since postinspiration is the phase of the breathing cycle with the lowest threshold for initiation of a pharyngeal swallow, removing or attenuating the descending influence of the KF in horizontal slices or in anesthetized mice may cause swallowing-related postinspiratory motor bursts to emerge, consistent with conditional, that is, not obligatory, PiCo activity in postinspiration (Bautista & Dutschmann 2014). Further, in the ventral medulla and pons, postinspiratory activity is readily observed within the KF but not seen in PiCo (Dhingra et al. 2020). Given these data, we cannot advocate that PiCo represents an independent third breathing oscillator, much less one essential for normal breathing or even for generation of breathing-related postinspiratory activity. Naming the entire area based on a function purportedly ascribed to a cluster of glutamatergic-cholinergic neurons is not at present warranted, especially in a region crowded with neuronal subpopulations, rhythmic networks, and breathing-related or coordinated functions, such as vocalization (Bautista et al. 2014, Deschênes et al. 2016, Wei et al. 2022); a neuroanatomical designation may be preferable.

Inhibition as an Essential Modulator of Breathing Pattern

Inhibition, although not essential for inspiratory rhythmogenesis (Funk et al. 1993, Wallén-Mackenzie et al. 2006, Janczewski et al. 2013), can profoundly affect breathing pattern (Cui et al. 2016, Cregg et al. 2017, Baertsch et al. 2018, Yang & Feldman 2018). About half of preBötC neurons are inhibitory, a mix of glycinergic and GABAergic neurons (Kuwana et al. 2006, Winter et al. 2009), some with intrinsic bursting properties in vitro (Morgado-Valle et al. 2010). Recurrent inhibition within, or afferent to, preBötC regulates the shape and peak inspiratory burst amplitude. That is why blockade of inhibitory synaptic transmission in vitro predominately affects burst amplitude, not frequency (Feldman &

Smith 1989, Shao & Feldman 1997, Brockhaus & Ballanyi 1998). In vivo, rhythm is slowed and burst amplitude is increased following blockade of inhibitory synaptic transmission in preBötC due to blocking signals originating in pulmonary afferents (Janczewski et al. 2013). Optogenetic activation of preBötC glycinergic neurons in vivo delays inspiration and produces apneas, while photoinhibition of these neurons increases tidal volume and shortens expiratory duration (Sherman et al. 2015).

Reciprocal inhibition in the bCPG prevents coactivation of inspiratory and expiratory muscles that would reduce the energy efficiency of normal breathing movements (but these muscles can be coactive, e.g., Valsalva maneuvers, which stabilize the trunk during heavy lifts and increase intraabdominal pressure for emesis or defecation). Inhibitory, mostly glycinergic, neurons in the Bötzinger complex (BötC), rostral to but distinct from the preBötC, provide phasic inhibition to preBötC and phrenic motoneurons during postinspiration and expiration (Speck & Feldman 1982, Feldman et al. 1984, Schreihofer et al. 1999, Ezure et al. 2003). Further, inhibition by pulmonary afferent input via the vagus nerve through NTS or volitional command can abruptly terminate inspiration, produce apnea, or permit other breathing-related motor patterns (Feldman 1986, Sherman et al. 2015, Cregg et al. 2017, Baertsch et al. 2018). Indeed, the preBötC receives significant inputs from the NTS that relay chemo-, baro-, and mechanoreceptor sensory signals, which arrive via the vagus, facial, and glossopharyngeal nerves and participate in expiratory or postinspiratory behaviors such as vocalization (Hernandez-Miranda et al. 2017). Related to the ability of inhibition to influence the respiratory phase, disinhibition of the BötC and preBötC in in situ preparations that generate a motor rhythm with distinct inspiratory, postinspiratory, and expiratory phases causes inspiratory and postinspiratory phases to fuse (Dutschmann & Paton 2002), even producing tonic activity on respiratory motor nerves (Marchenko et al. 2016). Note that such tonic activity in situ cannot be interpreted as vindication of synaptic inhibition being essential for rhythmogenesis (e.g., see Smith et al. 2007, Ausborn et al. 2018), because disinhibition dramatically raises excitability into a regime where preBötC neurons fire tonically and the preBötC loses its rhythmogenic capacity.

Suprapontine Afferents

In addition to connections within the bCPG and brainstem, multifarious inputs from suprapontine sites converge in the bCPG to convey sensory information and motor commands that modulate bCPG dynamics and coordinate breathing with other exigent behaviors (Figure 1). We focus on suprapontine projections to preBötC, while noting considerable connections to and from other components of the bCPG, for example, pF (Li et al. 2020) and KF/PBN (Figure 1a). Among projections affecting behaviors with an airflow component, (*a*) the periaqueductal gray integrates motor, limbic, and sensory information to modulate vocalization (Subramanian & Holstege 2010, Tschida et al. 2019). (*b*) Superior and inferior colliculi transmit visual and auditory signals that modulate breathing pattern (Keay et al. 1988). (*c*) Descending afferent projections from the forebrain reflect emotional, cognitive, and physiological states that impact breathing, for example, sighs and gasps with emotional valence. (*d*) Hypothalamic nuclei influence regulatory behaviors like feeding, body temperature, sleep/wakefulness, stress, and sex-specific behaviors such as mating and aggression (Kumar 2004, Harris & Aston-Jones 2006, Fontes et al. 2011, Sohn et al.

2013, Guzman-Ruiz et al. 2015, Kaur et al. 2017, Li & Dulac 2018). These regions are rich in neurons that secrete peptides and hormones such as ghrelin, orexin, and melanin-concentrating hormone, which can affect the breathing across different states (Benedetto et al. 2013). Bombesin-related peptide release during stress increases sighing, likely by affecting preBötC neurons with cognate receptors that also increase sigh rate (Li et al. 2016). (*e*) Primary and secondary motor cortex could provide efference copy to the preBötC for behaviors that need to be timed with the breathing cycle such as chewing, swallowing, and vocalization (Martin-Harris 2006, Bautista et al. 2014, Rea 2015). (*f*) Finally, central nucleus of the amygdala, associated with fear and stress responses (Ressler 2010, Fadok et al. 2018), can profoundly modulate breathing (Bonvallet & Gary Bobo 1972). In humans, electrical stimulation of the amygdala results in an apnea; this pathway may contribute to sudden unexpected death in epilepsy (Rhone et al. 2020).

BREATHING AND EMOTION

Our emotional and cognitive states affect breathing, such as when we are stressed, relaxed, or attentive to solving a problem. Reversing this causality, breathing can affect emotion and cognition both in ordinary day to day life and in more extreme/pathological conditions such as anxiety, fear, and panic (Figure 4). As you read this, during each inspiration, your pupil diameter is increasing (Borgdorff 1975, Melnychuk et al. 2018), your reaction time is faster (Schulz et al. 2016), your fear response is heightened (Zelano et al. 2016), your ability to encode and retrieve memories is more efficient (Heck et al. 2019), and you are less likely to initiate a volitional movement (Park et al. 2020), with the converse for all occurring during expiration (Figure 4) (for more examples, see Maric et al. 2020, Boyadzhieva & Kayhan 2021). Here, we focus on how breathing may change emotion and cognition and its therapeutic potential.

For millennia, controlled breathing practices informed by ancient spiritual traditions such as yoga and Tai Chi have been used to rebalance emotions and reduce stress in the long term (Nestor 2020, Lavretsky & Feldman 2021). There are also short-term benefits of controlled breathing as in Lamaze breathing for childbirth, which enhances relaxation and decreases pain perception, or in acute amelioration of panic attacks (Brown & Gerbarg 2005, Kamalifard et al. 2012, Chandla et al. 2013, Yuksel et al. 2017). Transient disruptions, that is, a single/few deep breaths/sighs, can also relieve everyday anxiety, for example, when looking up your grant score, when about to give a major address, or when getting ready to hit a drive off the first tee! Applications of breathing control are moving from culture to clinic. Training patients to control their breathing by modifying its rate and depth is effective in reducing negative emotional states such as depression, anxiety, and stress; reducing pain; improving visceral function; improving mood; and enhancing learning (e.g., Brown & Gerbarg 2005, Meuret et al. 2018, Weng et al. 2021).

That breathing can profoundly impact emotional and cognitive state in rodents and humans is supported by the presence of widespread breathing-modulated oscillations in local field potentials (LFPs) in many suprapontine regions (Karalis & Sirota 2022, Tort et al. 2018) (Figure 4). The working hypothesis is that these breathing rhythms entrain neuronal activity in networks that are critical to emotion, cognition, and memory (Figure 4), affecting signal

processing and/or binding information locally and across disparate brain regions (Tort et al. 2018, Heck et al. 2019), similar to roles ascribed to other LFP oscillations (Buzsáki 2006).

Nonbreathing brain rhythms, apart from δ in rodents, span frequency ranges much higher (δ: 1–4 Hz; θ: 4–8 Hz; α: 8–12 Hz; β: 13–30 Hz; γ: 30–150 Hz) than breathing at rest (humans: ~0.2 Hz; rodents: ~1–4 Hz). In humans, breathing rhythm differs from α, β, δ, θ, and γ oscillations because it (*a*) is continuously present for a different essential purpose, that is, gas exchange, and does not have to be separately generated within the brain; and (*b*) can be readily modulated by volition during breathhold, slow breathing in meditation, or fast breathing during hyperventilation. Put simply, we propose that as a readily available low-frequency signal, breathing rhythm was hijacked by the brain for its own signal-processing needs. The upshot is that volitional changes in breathing rhythm might be utilized to alter signal processing in one's own brain! We hypothesize that slow volitional breathing, as in regular meditation practice (chronic) or even a single or a few deep breaths (acute), including nonvolitional sighs, modulates temporal dynamics across interacting brain subnetworks to produce changes in emotional or cognitive state.

We envision at least six distinct pathways by which breathing can influence suprapontine structures associated with emotion and cognition (Figure 4). The first and second pathways are direct and indirect projections from the preBötC and other parts of the bCPG (Karalis & Sirota 2022). There are numerous direct projections from preBötC to suprapontine sites not normally associated with regulation of breathing (Yang & Feldman 2018, Yang et al. 2020) (Figure 1a); we propose that changes in breathing pattern originating in preBötC can, via mono- or polysynaptic projections, affect signal processing at sites associated with higher functions (Figure 1b). Projections to two pontine sites, LC and KF/PBN, are also powerful relays of breathing-related signals. Interfering with a direct projection from preBötC to LC, mediated by Dbx1-derived preBötC neurons (Bouvier et al. 2010, Gray et al. 2010) that express the cell adhesion molecule cadherin-9 (Cdh9), significantly changes mouse behavior (Yackle et al. 2017). Ablating Cdh9/Dbx1 neurons has no overt effect on viability, and breathing remains rhythmic and regular. There is, however, a change in the distribution of different breath types, shifting the distribution toward slower breaths associated with a shift to calmer behaviors. Further, Cdh9/Dbx1 ablation strengthens δ waves, an indicator of calmer mental state.

Third are breathing-modulated olfactory bulb oscillations, which transmit to brain regions associated with emotion (Zelano et al. 2016, Varga & Heck 2017, Karalis & Sirota 2022, Moberly et al. 2018, Tort et al. 2018, Bhattarai et al. 2021). Mechanosensory nasal signals that are by nature breathing modulated project throughout the brain, powerfully modulating suprapontine LFPs (Figure 4). These signals persist even in the absence of odors (Varga & Heck 2017, Tort et al. 2018), which suggests that olfactory pressure receptors generate and shape this rhythm.

Nasal breathing is more effective than oral breathing in modulating some behaviors. In mice, freezing behavior is degraded by disruption of olfactory bulb activity (Bagur et al. 2021). In humans, visuospatial tasks, memory recall, and surprise are enhanced during inspiration during nasal breathing but not during oral breathing (Zelano et al. 2016, Perl et al. 2019).

Nasal breathing appears more effective in memory consolidation, too, compared to oral breathing (Nakamura et al. 2018).

Despite these data, whether nasal airflow is necessary for these respiratory effects remains unsettled. Breathing entrainment of suprapontine neuronal spiking persists in many regions of the mouse brain after tracheotomy (Ravel & Pager 1990), where there is no nasal airflow, and following ablation of the nasal epithelium (Karalis & Sirota 2022). In humans, while some behaviors are significantly attenuated during oral compared to nasal breathing, lexical problem-solving is unaffected (Perl et al. 2019). Moreover, the essential differences in how rodents and humans use olfaction may limit the utility of generalizing rodent data to humans. Thus, it is challenging to discriminate between nasal and oral breathing or between olfactory and central breathing inputs as modulators of brain activity and associated behavior. Further investigations on the effects of perturbations, such as anosmia or tracheotomy, on brain activity and behaviors, such as fear conditioning, may delineate the effects of these pathways.

A fourth pathway is breathing-induced changes in pulmonary vagus nerve afferent activity (Noble & Hochman 2019). Stimulation of vagus nerve afferents can effectively alleviate symptoms of clinical depression in approximately 50% of individuals unresponsive to conventional therapies (Carreno & Frazer 2017). Among these stimulated afferents are pulmonary stretch receptors that terminate in the NTS, which in turn projects widely to brainstem sites that include the preBötC/bCPG. Activation of pulmonary afferents changes the breathing pattern via the Breuer-Hering lung inflation/deflation reflexes (see Feldman 1986). Whether these pulmonary afferent signals underlie rhythms seen in subcortical and cortical regions is unknown. Interestingly, vagal nerve stimulations can induce medial septum–mediated θ rhythm in the hippocampus (Broncel et al. 2018), which raises the possibility that θ and breathing rhythms interact via a circuit that includes the NTS (Tort et al. 2018).

Fifth, changes in blood gases, that is, significant deviation of CO_2 (Meuret et al. 2008, 2018) and O_2 above or below normal, can disturb emotional state. Abnormally high acute elevation of blood CO_2 invariably induces panic attack–like behavior in rodents (Banzett et al. 2021). Yet, chronic lowered blood CO_2—hypocapnia—is seen in approximately 70% of patients diagnosed with panic disorder and some other anxiety disorders (Meuret et al. 2008); raising their blood CO_2 to more normal levels by breathing exercises has a palliative effect on anxiety (Meuret & Ritz 2010). The effect of a single or a few deep breaths/sighs to induce calm is postulated to be due to acute lowering of CO_2. However, tissue CO_2 levels, unlike blood CO_2, are largely stable at short timescales such as one or two breaths, so experimental evidence for an acute effect via this mechanism at shorter timescales is required.

Sixth, descending volitional commands effecting breathing collateralize to regions involved in emotion and cognition. Breathing practice is affected by volitional command originating in cortex that takes over control of breathing muscles. Efference copy of these signals via intracortical or corticolimbic projections may directly affect regions involved in emotion and cognition. At present, very little is known about the pathways and mechanisms.

How could a practice of markedly altered breathing pattern therapeutically modulate emotion and cognition? For the sake of argument, assume that a particular dynamic state of activity in the interconnected networks of the limbic system generates the emotional and physiological state underlying anxiety. As activity reverberates in this network (Ozawa et al. 2020), connections strengthen, for example, by long-term potentiation (LeDoux 2000, Medina et al. 2002, Dalgleish 2004), accounting for the persistence of anxiety and a barrier to breaking down the network dynamics as a means to reduce anxiety. Therapeutic disruption of circuit dynamics to treat severe and otherwise intractable neurological conditions such as severe depression usually requires a heroic intervention such as electroconvulsive shock or deep brain stimulation (Dougherty 2018, Hermida et al. 2018, Drobisz & Damborská 2019). Because breathing rhythms are found in regions associated with emotion such as the limbic system (Karalis & Sirota 2022), they likely play a role in signal processing and/or binding in the circuits driving anxiety. We propose then that breathing can also be mobilized, much more benignly, to disrupt these circuits for stress and anxiety. When the normal breathing pattern is significantly altered, the gating of information across various networks involved in the anxiety pathway will be disrupted and, if done repeatedly over extended periods of time, could result in long-lasting changes in synaptic strength, for example, by long-term depression. The alterations in signal processing could be a direct effect of changes in the breathing-related rhythm or secondary to changes induced in faster rhythms such as δ and γ (Buzsáki 2004, 2006; Karalis & Sirota 2022).

RELEVANCE FOR OTHER MAMMALIAN NEURAL CIRCUITS

Looking forward, we highlight two questions at the forefront of neuroscience research that may be tractable in the bCPG: What dynamical mechanisms underlie microcircuit computations, and how do peptides modulate microcircuit behavior?

The rhythmic, patterned output of the bCPG masks the number of computations it performs to deliver breathing movements that maintain homeostasis amid an everchanging environment. For example, the preBötC continuously processes and integrates an array of sensory inputs such as lung mechanoreceptors, central and peripheral chemoreceptors, and volitional commands to encode the onset and duration of each inspiration. This functionality is required for many, much more elaborate behaviors, for example, those involved in processes underlying working memory (Durstewitz et al. 2000), action planning, and perceptual decision-making (Wang 2002). Our understanding of preBötC rhythmogenesis as an emergent property where short-timescale synchronization of the rhythmogenic neurons serves as a dynamic scaffold on which intrinsic and synaptic properties interact may therefore inform how such computations are implemented in other brain regions. Additionally, the coordination of breathing with so many other behaviors may serve to illustrate how microcircuits interact as dynamical systems. Rhythmic preBötC activity is passed on to (pre)motoneuronal populations through synchrony propagation, but the preBötC also provides a master clock signal for other brainstem CPGs (Kleinfeld et al. 2014). This integrated circuit of CPGs gates or coordinates activity across the spectrum of behaviors that use overlapping muscles to assure appropriate sorting of inhaled gases and ingested liquids and solids. The details of connections between subpopulations and the dynamical interactions of preBötC with other respiratory oscillators, with other orofacial

CPGs, and with suprapontine circuits involved in emotion and cognition are just beginning to be understood. Thus, developing and applying approaches for defining emergent and dynamical network properties, like tipping points, and comparing and contrasting neural mechanisms underlying breathing with other behaviors originating in different brain regions could reveal novel and fundamental commonalities in signal processing in the brain.

In every described neural circuit, there is molecular and functional heterogeneity of neuronal properties (Rathour & Narayanan 2019, Goaillard & Marder 2021); clearly this is the case for the preBötC. Diversity among preBötC neurons is evident in their expression of peptides or peptide-cognate receptors (Hayes et al. 2017). The heavy influence of peptidergic neuromodulation in the preBötC provides an intriguing opportunity to elucidate how a peptidergic modulatory layer of control expands the functionality and confers unique properties on mammalian neural circuits. Invertebrate CPGs show that peptidergic modulation of membrane properties and intracellular signaling pathways can result in surprising network-level dynamics (Marder 2011, 2012). Peptidergic pathways may also link breathing with other affective and cognitive functions and states, as has been demonstrated with μOR-expressing PBN neurons (Liu et al. 2022). Indeed, specific ties between a few peptides and particular breathing behaviors, for example, bombesin-related peptides and sighing (Li et al. 2016) and sneezing (Li et al. 2021, Liu et al. 2022), and pituitary adenylate-cyclase-activating polypeptide (PACAP) and airway protection (Shi et al. 2021), have been demonstrated, uncovering effects that may only be revealed under very specific physiological states and conditions. The endogenous roles for a number of other peptides such as endogenous opioids and how peptidergic signaling pathways may interact require further study but may be tractable in the preBötC (Niewoehner et al. 1983).

In summary, the apparent simplicity of breathing movements belies a complex neural control system with the twin properties of robustness and lability. The system exhibits diverse operational modes; coordinates breathing with a broad array of vital behaviors on a moment-to-moment basis; and interacts with neural circuits across the nervous system to modulate movement, emotion, and cognition. Elucidating the mechanisms that generate and control breathing presents opportunities for deeper understanding of neural circuits throughout the nervous system, as well as potential avenues for using breathing to improve well-being and mental health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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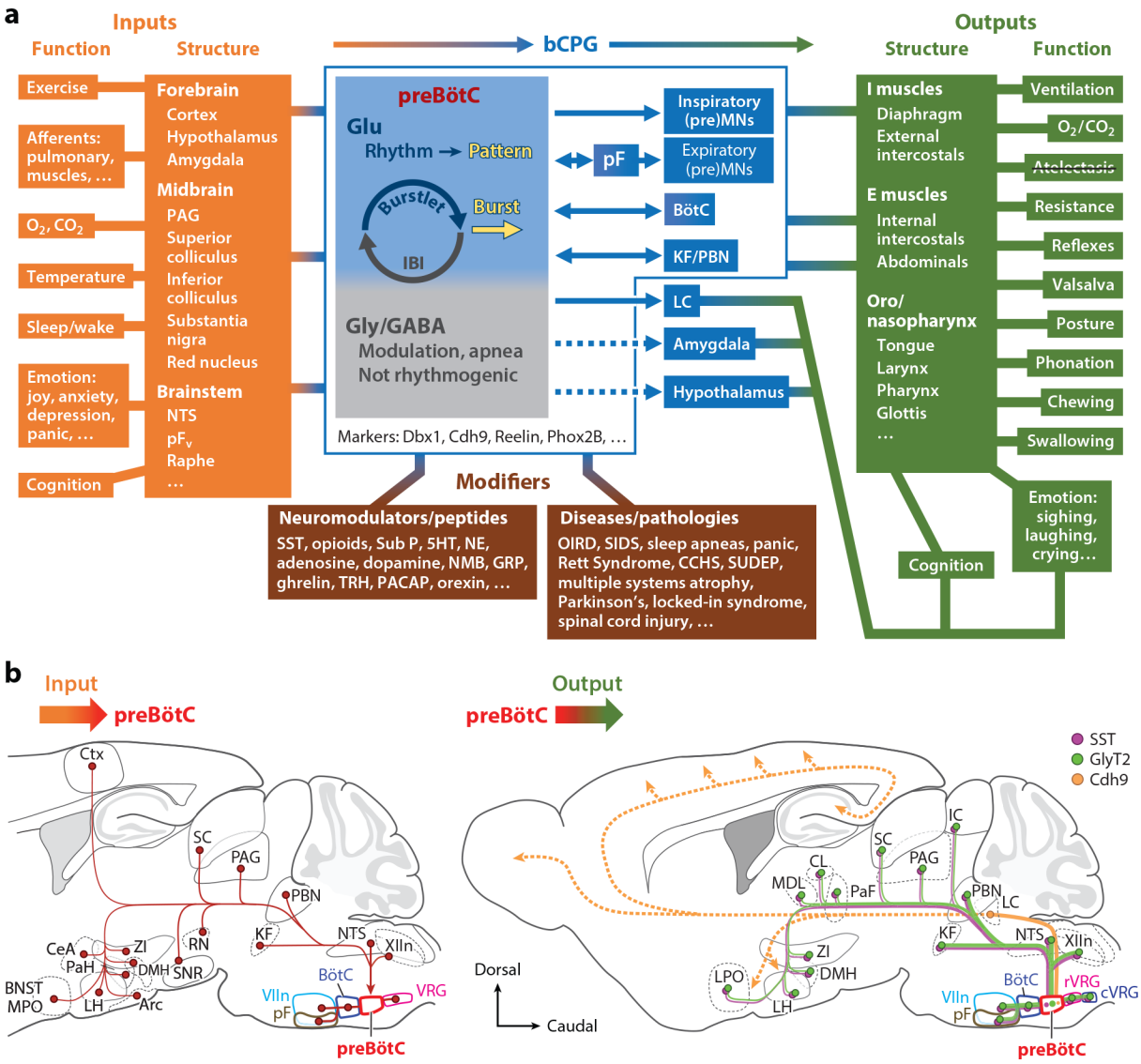

Figure 1.

Structural and functional organization of neural circuits controlling breathing. (*a*) Myriad physiological and neural functions feed information through a variety of structures into the bCPG to control breathing and respiratory-related behaviors (*orange*). At the core of the bCPG is the preBötC, which generates inspiratory rhythm and initiates inspiratory patterning and where approximately half of preBötC neurons are Dbx1-derived Glu neurons (*light blue*), while the other half are Gly/GABAergic (*gray*). Reciprocal connections between many bCPG structures produce the pattern of breathing and other respiratory-related behaviors. Molecular markers for some bCPG structures and their subpopulations are identified. bCPG activity is transmitted to a variety of muscles and other brainstem and suprapontine circuits to mediate or modulate many behaviors (*green*). Neuromodulators and peptides as well as a number of diseases (*brown*) (Supplemental Appendix, Note 1) may modify or alter bCPG function. (*b*, *left*) preBötC receives afferent input from brainstem and suprapontine sites (*dark red*). (*Right*) SST^+ (*purple*), $GlyT2^+$ (*green*), and Cdh9 (via

LC, *orange*) preBötC neurons project throughout the brain to relay breathing information directly (*solid lines*) or indirectly (*dotted lines*) to higher-order brain regions with some connected reciprocally. Note that all boundaries and projections are schematic and not intended to represent actual anatomical localization or relationships between neuronal populations, regions, or connections. Abbreviations: Arc, arcuate nucleus; bCPG, breathing central pattern generator; BNST, bed nucleus of the stria terminalis; CCHS, congenital chronic hypoventilation syndrome; Cdh9, cadherin-9; CeA, central amygdala; CL, central medial thalamus; Ctx, cortex; cVRG, caudal ventral respiratory group; Dbx1, developing Brain Homeobox Protein 1; DMH, dorsomedial hypothalamus; Glu, glutamatergic; Gly, glycinergic; GRP, gastrin-releasing peptide; IC, inferior colliculus; KF, Kölliker-Fuse; LC, locus coeruleus; LH, lateral hypothalamus; LPO, lateral preoptic area; MDL, medial dorsal thalamus; MN, motoneuron; MPO, medial preoptic area; NE, norepinephrine; NMB, neuromedin B; NTS, nucleus of the solitary tract; OIRD, opioid-induced respiratory depression; PACAP, pituitary adenylate-cyclase-activating polypeptide; PaF, parafascicular thalamus; PAG, periaqueductal gray; PaH, paraventricular hypothalamus; PBN, parabrachial nucleus; pF_V, parafacial ventral; Phox2b, paired Like Homeobox 2B; preBötC, preBötzinger complex; RN, red nucleus; rVRG, rostral ventral respiratory group; SC, superior colliculus; SIDS, sudden infant death syndrome; SNR, substantia nigra; SST, somatostatin; SUDEP, sudden unexpected death in epilepsy; TRH, thyrotropin-releasing hormone; VIIn, facial nucleus; VRG, ventral respiratory group; XIIn, hypoglossal nucleus/nerve; ZI, zona incerta.

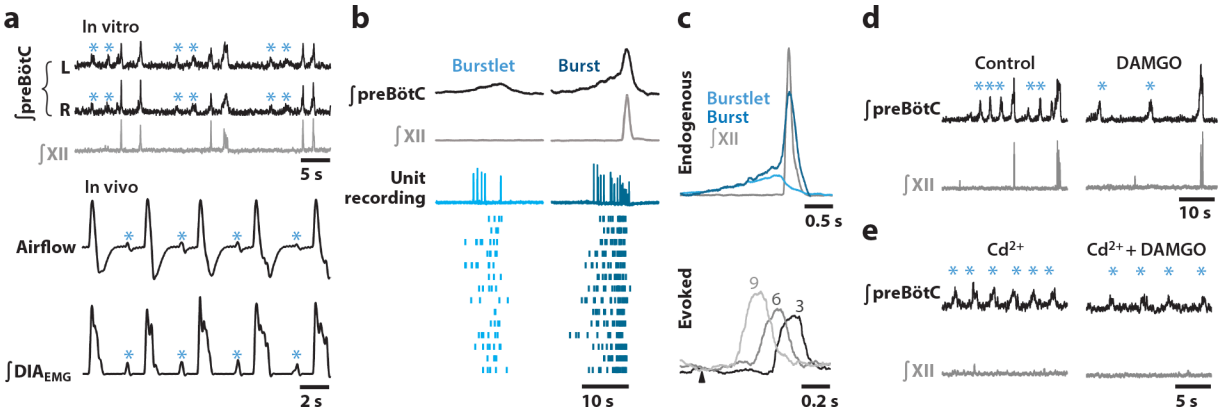

Figure 2.

Burstlets point to an emergent rhythmogenic mechanism in preBötzinger complex (preBötC). (*a*, *top*) Lowering excitability elicits bilaterally synchronous burstlets (*cyan asterisks*) and bursts in simultaneous in vitro recordings of hypoglossal (XII) nerve roots (*gray*) and ipsi- and contralateral preBötC (*black*) population activity. (*Bottom*) Small bursts (*cyan asterisk*) between inspiratory bursts that resemble leak through of burstlets observed in vitro can be observed following injections of excitants in in vivo recordings of airflow and diaphragm electromyograms (EMGs) in anesthetized, vagotomized adult rats. (*b*) Average burstlet and burst from preBötC and XII population recordings in vitro along with a cell-attached recording of a preBötC neuron, showing representative firing and raster plots during burstlets (*cyan*) and bursts (*teal-aquamarine*), where each line of each column represents action potentials of the recorded neuron during instances of burstlets and bursts. (*c*, *top*) Superimposed average waveforms of XII bursts and preBötC burstlets and bursts during endogenous rhythm in vitro indicate significant overlap in burstlets (*cyan*) and the preinspiratory rising phase (*teal-aquamarine*) of bursts. (*Bottom*) Sample of XII inspiratory bursts in vitro is shown as a function of number of neurons stimulated by holographic photolysis of caged glutamate. (*d*,*e*) The μ-opioid receptor agonist DAMGO depresses the frequency of burstlet-burst rhythms, elicited by lowered excitability (*d*), and burstlet-only rhythms, elicited by low Cd^{2+} (*e*), consistent with burstlet theory. Panels *a*–*d* adapted from Kam et al. (2013a,b); panel *e* adapted from Sun et al. (2019).

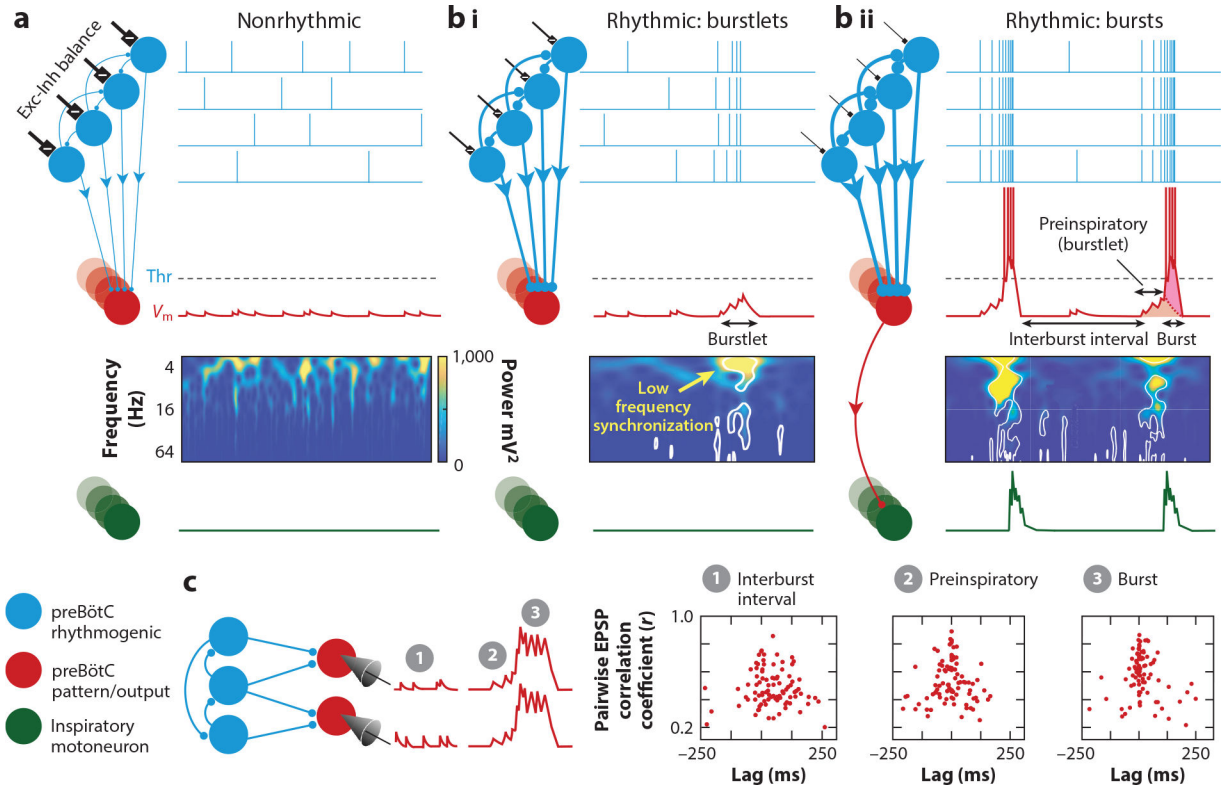

Figure 3.

preBötzinger complex (preBötC) synchronization, gated by background excitation-inhibition (Exc-Inh) balance, drives rhythmicity. (*a*, *b*) Connection scheme (legend at *bottom left*) with firing pattern of rhythmogenic neurons, membrane potential (V_m), and time-frequency decomposition of the V_m trajectory from an output neuron (*red*) recorded in vitro. (*a*) When background Exc-Inh balance is tilted toward Inh, rhythmogenic neurons (*cyan*) spike spontaneously but fail to synchronize, so no collective rhythmicity emerges in the preBötC, as revealed by the power spectra, which exhibit disconnected color patches (increased power) in the low-frequency range of 4–8 Hz. Due to asynchronous inputs, the V_m of output neurons does not cross threshold or generate network output. (*b*, *i*) When the background Exc-Inh balance tilts toward Exc, recurrently connected rhythmogenic neurons begin to synchronize, facilitating preBötC burstlet rhythm. Output neurons show a significant increase in low-frequency (4–8 Hz) activity during a burstlet, which reflects emerging synchronization in preBötC resulting in increased synaptic drive onto output neurons. Nascent synchronization at this stage does not cross the tipping point to propagate to (pre)motoneurons (*green*) to elicit a motor output. (*ii*) Further shift of background Exc-Inh balance enhances the ability of rhythmogenic neurons to synchronize strongly. Synaptic inputs onto output neurons show a progressive increase in power from low to higher frequencies (4–64 Hz) as the network assembles from preinspiration to the inspiratory burst. When network synchrony crosses the tipping point, the output neuron crosses a threshold (Thr), and an inspiratory burst occurs; activity during the burst propagates to motor output. Here, the burstlet is recognized as preinspiratory activity because it leads inexorably to the inspiratory burst. White contours in the spectrograms in subpanels *i* and *ii* enclose

regions with significantly increased power as compared to the control in panel *a* at 95% confidence level. (*c*) Simultaneous recordings from pairs of output neurons (*red traces*) illustrate synchronization of their synaptic inputs via their pairwise excitatory postsynaptic potential (EPSP) correlograms (*right*) as the cycle evolves from interburst interval (①) to preinspiratory (②) to inspiratory burst (③) phases. Spectrograms adapted from Ashhad & Feldman (2020).

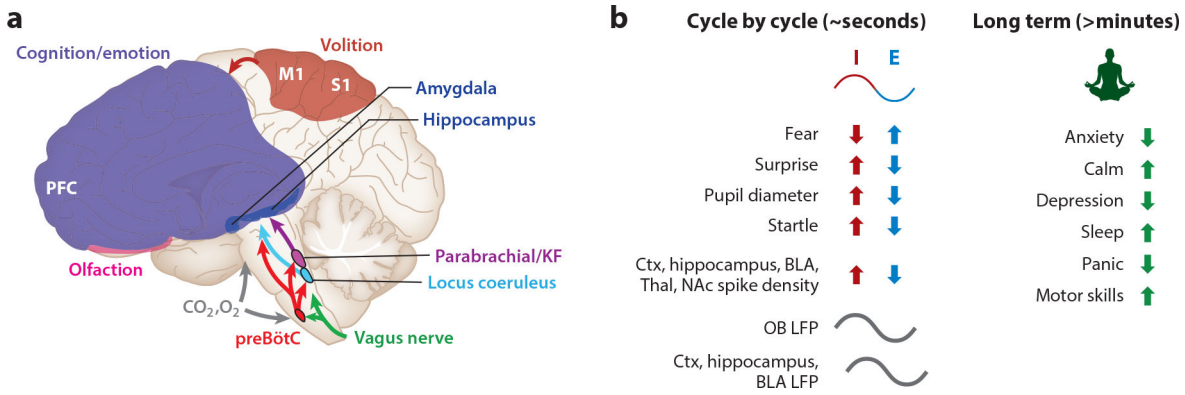

Figure 4.

Breathing influences cognition and emotion through global entrainments of interacting brain circuits. (*a*) Forebrain regions involved in cognition/emotion, for example, PFC, amygdala, and hippocampus, can be modulated by breathing signals from a variety of sources. (*b*) The global breathing rhythm modulates behavior through entrainment of local neuronal dynamics and breathing-locked LFPs across several brain regions on a cycle-by-cycle basis (*left*) and through plasticity affected by breathing practices (*right*). Note that all boundaries and projections are schematic and not intended to represent the actual anatomical localization or relationship between neuronal populations, regions, or connections. Abbreviations: BLA, basolateral amygdala; Ctx, cortex; KF/PBN, Kölliker-Fuse/parabrachial nucleus; LFP, local field potential; M1/S1, primary sensorimotor cortex; NAc, nucleus accumbens; OB, olfactory bulb; PFC, prefrontal cortex; Thal, thalamus.