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Review article

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Global coordination of brain activity by the breathing cycle

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Abstract

Neuronal activities that synchronize with the breathing rhythm have been found in humans and a host of mammalian species, not only in brain areas closely related to respiratory control or olfactory coding but also in areas linked to emotional and higher cognitive functions. In parallel, evidence is mounting for modulations of perception and action by the breathing cycle. In this Review, we discuss the extent to which brain activity locks to breathing across areas, levels of organization and brain states, and the physiological origins of this global synchrony. We describe how waves of sensory activity evoked by nasal airflow spread through brain circuits, synchronizing neuronal populations to the breathing cycle and modulating faster oscillations, cell assembly formation and cross-area communication, thereby providing a mechanistic link from breathing to neural coding, emotion and cognition. We argue that, through evolution, the breathing rhythm has come to shape network functions across species.

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Introduction

Four hundred million years ago, the emergence of rhythmic air-breathing enabled vertebrates to transition successfully from aquatic to terrestrial environments. Since then, animals in these taxa have evolved under the uninterrupted lull of alternating inspirations and expirations. Along this evolutionary journey, various secondary adaptations arose that are directly or indirectly linked to the respiratory cycle. Prominent examples include the use of airflow from exhalations to produce the sounds that mould social interactions and the evolution of olfaction to sense the molecules that inhalations bring in. One idea that is gaining recognition is that the brain has also adapted to make use of breathing as a global synchronizing signal that modulates neuronal activity[1–4]. This synchrony occurs throughout the brain, affecting brain regions and functions not typically associated with breathing, such as the neocortex, amygdala (AMY) and hippocampus (HC) (and hence decision-making, fear processing and memory formation)[5–7].

Recent discoveries have begun to illuminate the impactful nature of breathing-coupled neuronal activity across species and brain regions. In this Review, we aim to provide a comprehensive description of the mechanisms by which breathing cycles recruit brain activity and explore how these can give rise to known respiratory modulations of brain function, drawing from studies in human and non-human animals. We begin by describing the evidence for breathing effects across various levels of brain organization, from individual cells to large-scale networks. Next, we delve into the possible sources of this global breathing–brain synchrony, weighing current evidence to identify the primary contributors. We then explore sensory, emotional, cognitive and behavioural processes modulated by the respiratory cycle. As we will show, this field is quickly beginning to propel our understanding of how reciprocal brain–body interactions shape neuronal function, with implications for both basic neuroscience and translational research.

Breathing–brain synchrony across scales

Animal studies have long established oscillatory activity synchronous with breathing as a fundamental feature of neural circuits in the olfactory system[8–13] (for reviews, see refs. 14–17). It was demonstrated early on that these rhythmic changes in extracellular potentials were not merely artefacts caused by breathing movements. However, it has taken several decades for neuroscientists to realize that the influence of the breathing rhythm extends far beyond respiratory and olfactory domains, affecting neuronal activity across multiple timescales, levels of organization (Fig. 1) and brain areas in animals and humans[5,6,18–43]. These discoveries were made possible by advances in digital signal analysis, which provided methods to rigorously quantify breathing modulation (Box 1).

Modulation of single-cell activity

Rhythmic breathing is well known to induce cyclical modulations of neuronal activity in the olfactory system, including the olfactory epithelium, the olfactory bulb (OB) and the primary olfactory (piriform) cortex, where they have been functionally linked to sensory processing in rodents and humans[44–50]. In these regions, both local and projecting neurons exhibit subthreshold membrane potential oscillations and spiking coupled to breathing[44–48]. Beyond the olfactory system, a handful of studies have demonstrated respiratory influence at the subthreshold membrane potential level[6,26,32,51,52] (Fig. 1). Specifically, using intracellular recordings in head-fixed, anaesthetized rodents, prominent membrane potential oscillations phase-locked to breathing cycles have been observed in neurons in the prefrontal cortex (PFC)[51], primary sensory cortex[51], parietal cortex[6,32,52], HC[26] and primary visual cortex[51].

The study with the largest sample size — 69 neurons from 4 non-olfactory regions: the HC, medial prefrontal cortex (mPFC), primary sensory cortex and primary visual cortex — found that a significant percentage (>65%) had their membrane potential modulated by the slow breathing regime seen during anaesthesia[51]. For these neurons, the episodes of subthreshold, breathing-coupled membrane potential oscillations were often intermittent, lasting at most a couple of seconds[51]. These intracellular observations match results obtained at the network level, which typically show transient effects of breathing; indeed, episodes of breathing-related oscillations in the membrane potential and field potential levels tend to coincide[6,26,32,51,52].

Intracellular recordings also showed that neuronal discharges are modulated by breathing cycles, with spikes typically occurring at the peak of the depolarization phase of the breathing-coupled membrane potential oscillations[6,26,32,51,52]. Juxtacellular recordings confirmed the modulation of spike emission by breathing and extended the findings from anaesthetized animals to head-fixed animals, with effects seen in non-olfactory regions that include the HC[27], prelimbic and infralimbic cortices[32], parietal cortex[32] and orbitofrontal cortex[25]. Nevertheless, most evidence for spiking modulation comes from extracellular recordings of single and multi-unit activity in awake animals[5,18,19,23,25,29,39,52,53] (Fig. 1). Combined, this multitude of animal studies has shown that neurons in virtually all recorded regions show some degree of spike–phase coupling to breathing, including subcortical regions such as the thalamus, striatum and AMY[5]. In humans, the only study of this kind — performed during surgery for deep brain stimulation — found spike modulation by breathing in the thalamus and subthalamic nucleus[54].

In rodents, breathing modulates both excitatory and inhibitory cells, with the latter showing a greater percentage of modulated neurons[5,29,39]. The preferred phase of the breathing cycle within which spiking occurs varies across neurons, but there are population tendencies that depend on the cell's location, type and functional role, as well as the breathing rate and behavioural state[5,39,52,53]. For example, interneurons and pyramidal cells tend to spike during different breathing phases[29,39], as do neurons that are differentially modulated by fear[19].

Modulation of network activity

Breathing–brain interactions can also be observed at the level of neuronal populations. A commonly studied signal at the network level is the local field potential (LFP), which reflects voltage fluctuations in the extracellular space arising from the summed synaptic activity of neurons near the recording electrode[55]. LFP activity is often oscillatory; different brain circuits can generate neuronal oscillations within various frequency ranges, dictated by the physiological time constants of the underlying synaptic processes[56–58]. Among them, classical oscillations include thalamocortical delta (0.5–4 Hz), septo-hippocampal theta (6–10 Hz) and local gamma (30–120 Hz) rhythms[58].

Slow network activity driven by breathing

In the OB and olfactory cortex, the breathing rhythm has long been known to induce slow oscillations in the LFP that are phase-locked to its cycles[12], and therefore follow the instantaneous breathing frequency (1–12 Hz in rodents)[59]. More recently, similar breathing-coupled LFP oscillations have been reported in non-olfactory areas in rodents[18,26] (Fig. 1). Initially, low-frequency oscillations in the mouse whisker

barrel cortex were shown to be phase-locked to respiration[18], and a similar phase-locking was found for slow LFP oscillations in the dentate gyrus of the mouse HC[26]. As in the olfactory system, these oscillations were coupled to the breathing frequency on a cycle by cycle basis: that is, any changes in breathing frequency resulted in an immediate change in LFP oscillation frequency (within a single breathing cycle).

A surge of animal research during the past decade has confirmed and expanded the findings of respiratory coupling in non-olfactory regions[5,6,19,20,24,29,30,32,33,36,43,60]. These include neocortical areas spanning the prefrontal, parietal and visual cortices, and subcortical structures such as the ventral HC, thalamus, striatum and AMY[5,6,20,43]. Phase-locking of field potentials to breathing was also found in the human brain through scalp electroencephalography (EEG)[61] and intracranial recordings[34,35], with the latter identifying coupling in areas including the lateral and medial orbitofrontal cortex, anterior cingulate cortex, insula, premotor and parietal cortices, HC and AMY[34,35]. A technical note is in order, though: as for any other LFP component, breathing-coupled oscillations may not reflect local network activity in the region in which they are detected and could instead be due to volume conduction from distant current sources[6]. Furthermore, for any given brain region, breathing-coupled LFP oscillations are not always present; although they are known to depend on the brain state[24] (Box 2), the possible triggers, gating mechanisms and neuromodulators leading to their appearance remain to be fully understood.

Because of their overlap in frequency range, observations of rhythmic synchrony between breathing and LFPs in animal studies were initially interpreted as evidence for respiratory coupling of endogenous delta and theta oscillations[62,63]. However, as we will discuss below, breathing gives rise to distinct LFP components that can coexist with these other network oscillations.

Modulation of gamma rhythms and cell assemblies

Breathing also influences faster network oscillations. In the OB and olfactory cortex of animals and humans, bouts of prominent gamma oscillations emerge within each breathing cycle[16,64]. The amplitude of these fast oscillations is modulated by the respiratory phase and their generation depends on olfactory drive[5,64–67].

In rodents, all respiratory frequencies modulate oscillations in the 70–110 Hz gamma sub-band[32,59,68]. During awake immobility, breathing–gamma coupling can be observed throughout the brain[6,18,20], being more prominent in frontal regions[5,6,29,32]. In these quiet awake states, respiratory coupling appears in a comodulogram as the modulation of the amplitude of the gamma oscillations by a delta-frequency oscillation. During exploratory states associated with prominent septo-hippocampal-generated theta oscillations, different patterns of phase–amplitude coupling can be observed across the brain, with more posterior regions tending to show coupling between theta and gamma oscillations, and anterior regions displaying breathing–gamma coupling[32]. Interestingly, the gamma oscillation sub-bands modulated by theta oscillations and breathing differ, suggesting that distinct frequency channels transmit different types of information[32]. Because breathing is faster during active states, breathing–gamma coupling may appear as theta-frequency modulation of the gamma oscillation amplitude in comodulograms. Therefore, without accompanying breathing recordings, breathing–gamma coupling in frontal regions could be mistaken for theta–gamma coupling[1]. A helpful criterion for differentiating between these mechanisms is that theta–gamma coupling is strongest during rapid eye movement sleep[69,70], whereas breathing–gamma coupling is mostly absent during sleep[21,32,43], consistent with a substantial reduction of olfactory-driven gamma activity[21,43,67,71,72].

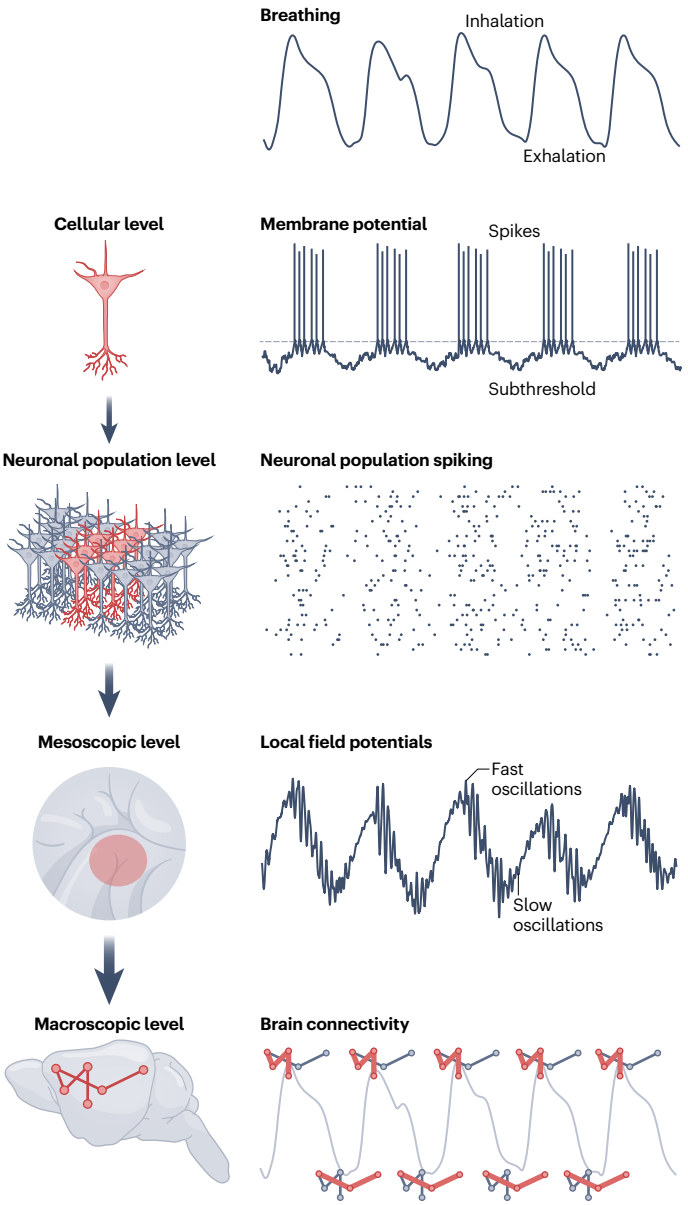


Fig. 1 | The modulation of neuronal activity by breathing across scales. At the cellular level, breathing modulates the subthreshold membrane potential of neurons, thereby controlling excitability and spike emission[51,52]. At the neuronal population level, breathing modulates the spiking activity of different groups of cells that transiently co-activate, known as cell assemblies[66]. At the mesoscopic level, breathing drives both slow and fast local oscillations, readily evidenced in raw local field potential traces[1,6]. At the macroscopic level, breathing influences large-scale communication across distributed brain networks[5,22,78]. All images are illustrative schematics.

In addition to the robust modulation of 70–110 Hz gamma oscillations, breathing may also modulate the slower 35–60 Hz gamma sub-band in rodents[14,67,68,73]. Breathing–slow gamma coupling mainly occurs during slow respiratory regimes, is particularly prominent in the

Box 1 | Unveiling synchrony between brain activity and breathing

To infer that a given brain signal is synchronous with breathing, respiratory activity must first be monitored. Several tools are available to record breathing[271], including pressure sensors, temperature probes, electromyographs (used to record the activity of respiratory muscles), plethysmographs (used to monitor airflow), face masks, infrared cameras, piezoelectric devices (movement sensors) and electrocardiographs. In non-human animals, direct recordings from the olfactory epithelium reliably track breathing cycles[272]. Alternatively, olfactory bulb (OB) activity can be measured and used as a proxy for breathing; however, the OB does not always exhibit breathing-coupled activity[271], particularly during deep sleep and anaesthesia (when slow oscillations dominate OB activity and may be mistaken for the breathing-coupled rhythm)[28].

These measures of breathing can be obtained simultaneously with recordings of neural activity. Having done so, clear criteria are required to establish synchrony, and these will depend on the nature of the brain signal under analysis. For local field potentials (LFPs), breathing-coupled rhythms are defined by two criteria[1,6]: the presence of an LFP power peak that matches the frequency of the breathing rate; and significant phase coherence between the LFP and the respiratory signal at this frequency. The latter can be assessed by constructing a null distribution of coherence values using randomly circular-shifted LFP and breathing signals or mismatched breathing and brain signals from different trials or subjects[6]. The same criteria can be applied to other continuous brain signals (such as those recorded via electroencephalography (EEG), electrocorticography, intracranial EEG or magnetoencephalography). We note that autocorrelograms and cross-correlograms should yield comparable results with those of power and coherence analyses, given their mathematical interdependence. However, assessing standard correlation between breathing and brain signals is less advisable, as their coupling may be missed due to non-zero phase lags between the signals. Moreover, the standard correlation is already captured by the cross-correlogram at the zero lag.

An alternative approach to detect breathing–brain synchrony involves the use of event-triggered averages[34,100]. In this method, inhalation peaks (or any other landmark of the breathing cycle) serve as reference time points and the brain signal is averaged centred around these points — that is, signal segments centred on each reference point are extracted and averaged across multiple breathing cycles. If breathing does not modulate the signal, the averaged trace will be roughly flat, as non-time-locked fluctuations will be cancelled out. Conversely, breathing modulation appears as a fluctuation in the averaged signal that aligns with the respiratory cycle. Similar to other signal analysis techniques, event-triggered averages are susceptible to finite sample size bias — with fewer samples, non-breathing-related signal fluctuations may produce an apparent, albeit false, modulation in the average trace. Thus, the fluctuations in inhalation-averaged brain signals should be statistically tested against chance. Similar to the statistical analysis of phase coherence, this can be achieved by generating randomized circular time shifts between the signals and recalculating inspiration-averaged traces to form a null distribution.

Both of these approaches can also be used to infer synchrony between breathing and faster brain signals, such as spiking activity or instantaneous gamma amplitude. For spiking, synchrony can also be assessed through phase-distribution analyses, in which spike–phase histograms are generated by counting spikes within different phase bins of the respiratory cycle, followed by statistical analysis to determine whether the observed spike–phase distribution deviates from chance. However, caution is required owing to the non-sinusoidal shape of breathing waveforms[5], which results in a non-uniform distribution of breathing phases; the longer duration of expiration means that even non-modulated neurons will emit more spikes during this phase — thus, corrections must be applied. The phase-distribution approach can also be used to quantify the breathing modulation of other electrophysiological events that have discernible 'time stamps', such as ripples, dentate spikes, spindles and up–down state transitions.

Similarly, the average amplitude of gamma oscillations (or any oscillation faster than breathing) can be computed across respiratory phases, and the mean fluctuation quantified and statistically tested against chance[273]. Furthermore, breathing-phase LFP–amplitude comodulograms can be generated that visualize modulation indices as a two-dimensional heat map across multiple breathing and LFP frequencies[1]. Beyond these analyses, higher-order metrics such as interregional synchrony[22,274] and patterns of functional connectivity[78] can also be examined in relation to the breathing phase. Lastly, although most research has focused on phase-locked modulation of brain activity by the breathing cycle, other types of breathing–brain interactions occur, such as relationships between brain activity and the breathing frequency[41] or peak flow rate[24], which require a different set of analytical methods for assessment.

olfactory cortex[66,74,75] and has also been observed in subcortical regions such as the AMY[5] and the striatum[75]. When present, the modulated slow gamma oscillation tends to arise later in the breathing cycle and to be more closely associated with expiration than inspiration[14,73].

In intracranial recordings from people with epilepsy, broadband gamma power (40–150 Hz) has been found to be modulated by breathing in the OB, olfactory cortex, AMY, HC, insula, cingulate, orbitofrontal cortex, and motor and parietal cortices[35]. In humans, whose breathing (at ~0.3 Hz) is slower than that of rodents, breathing also modulates lower frequencies, including delta, theta, alpha and beta[34,50,76]. Widespread respiratory phase–amplitude modulation across frequencies has also been reported in resting-state magnetoencephalography recordings[77], and in alpha and beta EEG frequencies during visuo-spatial tasks[78]. Identifying breathing effects through functional MRI can be challenging as breathing produces artefacts in the blood oxygenation level-dependent signal[79] and breathing-related fluctuations are thus usually removed during preprocessing[80]. Nevertheless, recent work has shown that breathing–brain coupling can also be detected with functional MRI[81,82].

Gamma oscillations are associated with local network computations and the formation of cell assemblies[83,84] — functional groups of neurons that transiently co-activate[85]. Recent work in the mouse olfactory cortex has demonstrated that breathing-driven gamma oscillations emerge from local inhibition exerted by feedback interneurons

and that these give rise to sparse cell assemblies of the most active cells (those that escape this inhibition)[66]. By pacing a winner-take-all mechanism, breathing can thus modulate local network computations. Similar mechanisms might take place in other cortical regions[86], although gamma oscillations are also associated with other mechanisms of neuronal coding[87], through which breathing might also be hypothesized to alter computations (see 'Orchestration of interregional communication'). Beyond the olfactory cortex, the breathing phase (or the related 4 Hz LFP rhythm) modulates cell assemblies within the rodent mPFC[38,88] and between the mPFC and the striatum[89], with interneurons and gamma oscillations having a role in shaping assembly activity[4,38,88,89]. As slow oscillations have widespread phase coherence and can aid long-range communication[90,91], breathing–gamma coupling could enable the integration of the activity of cell assemblies generated transiently in distributed cortical regions during each respiratory cycle.

Orchestration of interregional communication

Gamma oscillations have classically been associated with binding neuronal representations across regions and supporting cortical computations[92]. During wakefulness in mice, rats and cats, the breathing rhythm not only modulates gamma amplitude but also influences long-distance gamma coherence[21,22,43]. Specifically, variations in gamma synchrony that depend on the breathing phase have been reported between the OB and the frontal[21,22], somatosensory, posterior parietal and visual cortices, as well as among these neocortical regions[21]. The breathing phase also modulates gamma synchrony between the mPFC and the thalamic nucleus reuniens[43].

Recent evidence demonstrates that breathing can directly influence spike transmission between distinct brain regions. Such inter-area communication can be studied by identifying linear combinations of neurons that maximize cross-regional correlations of spiking activity, referred to as communication subspaces[93]. Breathing strongly modulates the activity of the communication subspace between the mouse OB and olfactory cortex and parses feedforward and feedback interactions into distinct phases of its cycle[94]. This suggests that breathing acts as a temporal scaffold, orchestrating neuronal communication by aligning network dynamics and facilitating coherent interactions.

In mice, the breathing phase also influences hippocampo-cortical interactions by modulating the occurrence of sharp-wave ripples (SWRs)[5,31], a characteristic hippocampal activity pattern involved in the replay of neuronal sequences and cortical consolidation of memory traces[95]. Interestingly, the spiking response of neocortical neurons to hippocampal ripples depends on the breathing phase, as does the amount of coincident spiking between hippocampal and neocortical units[5]. Breathing further modulates the generation of dentate spikes[5], sharp positive deflections of the hilus LFP driven by entorhinal cortex inputs[96] and implicated in associative learning[97,98]. Both SWRs and dentate spikes occur during rest and slow-wave sleep — 'offline' states in which the brain disconnects from external sensory stimuli and processes internal information. In the cortex, the breathing phase modulates the onset of other offline network patterns known as up states and down states[5], alternating periods of global depolarization and hyperpolarization of the neuronal population[99]. Similar findings have been reported in humans, where the breathing phase modulates 'sleep oscillations' (ripples, spindles and slow-wave activity)[100–102]. Moreover, breathing modulates changes in human functional connectivity, measured via EEG, during rest[78]. Therefore, current evidence suggests that the breathing rhythm paces the dynamics of the internal computations performed by distributed neuronal circuits during offline states[5].

Relationships between breathing frequency and network oscillations

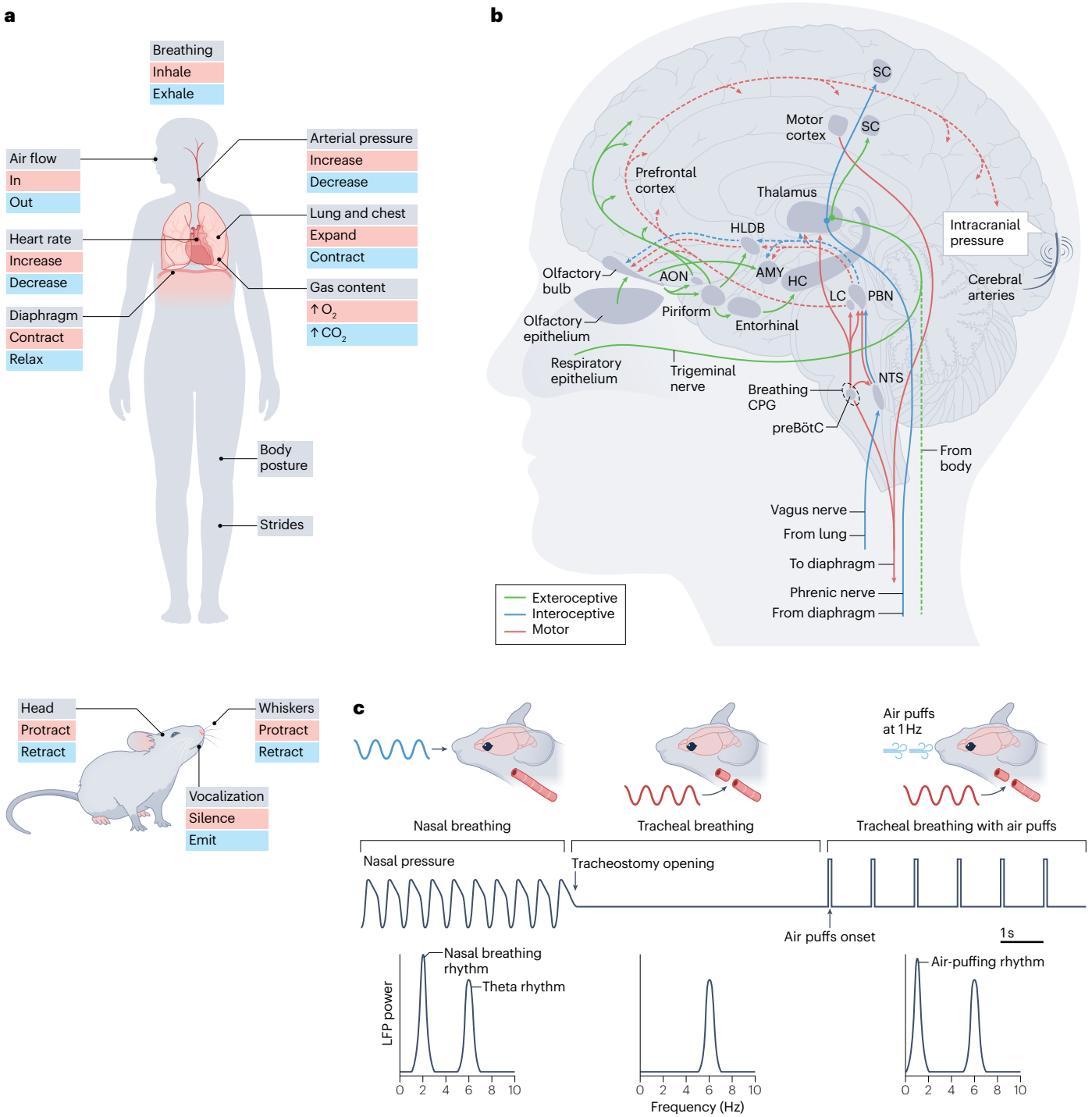
Emerging evidence indicates that breathing–brain interactions extend beyond phase-locking relations. On a slower timescale, spanning several respiratory cycles, the frequency of breathing in mice was found to positively correlate with the frequency of both theta and gamma oscillations[41]. Interestingly, changes in theta frequency preceded changes in the breathing rate, and changes in gamma frequency followed them[41]. It is plausible that a common drive, possibly from brainstem nuclei, sends arousal signals to brain networks and respiratory muscles, with theta changes occurring first due to shorter synaptic and conduction delays in the pathways that mediate these

Box 2 | Breathing-coupled oscillations depend on the brain state

The influence of breathing on neuronal activity depends on the brain state[21,22,24,32,36,39,43,53]. During wakefulness, which includes periods of active exploration and immobility, breathing-coupled oscillations can be observed across the rodent brain but exhibit a pronounced antero-posterior gradient, with stronger synchrony in anterior olfactory and frontal regions[6,24,32]. Notably, in posterior brain regions, breathing synchrony increases during immobility compared with periods of exploration[24,32].

Is immobility a state that particularly favours respiratory coupling? Recent findings suggest that quiet wakefulness is characterized by long and deep inspirations, which may facilitate the coupling of breathing oscillations across the brain[24]. During exploration, however, animals exhibit faster and more variable breathing and/or sniffing frequencies — ranging from 5 Hz to 14 Hz in mice (compared with 1–3 Hz during immobility)[5,6,27,215]. This non-stationary instantaneous breathing frequency may 'dilute' coherence levels across the faster breathing range, making it difficult to detect. Additionally, theta oscillations are prominent during exploration and often overlap with the breathing frequency range[6,27]. As theta activity is not phase-locked to breathing, this overlap masks breathing coherence measured via signal analysis during active behaviours[1]. These observations do not exclude the possibility that neuronal activity is less coupled to breathing during active states, but do suggest that technical challenges must be taken into account when evaluating breathing–brain interactions in active states.

Irrespective of changes within awake states, it is clear that brain synchronization with breathing decreases considerably during sleep compared with wakefulness[21,22,24,32,36]. Nevertheless, several rodent studies still report statistically significant breathing-coupled oscillations during sleep[6,24,32,36,41] (albeit at lower synchrony levels than those seen during wakefulness), suggesting they may still have a functional role in offline states. The effect of sleep is most pronounced for olfactory-driven gamma activity[67,71,72] and breathing–gamma coupling, both of which are drastically reduced[21,32,43]. These findings suggest that neuromodulatory systems may be responsible for the changes in breathing effects across sleep–wake states. A particular candidate is the locus coeruleus noradrenergic system, whose activity decreases during sleep[116] and may thus influence breathing-related neural synchrony.



oscillations. By contrast, gamma activity depends on a reafferent drive and thus follows changes in breathing rate. Notably, the frequency of the amplitude-modulated fast gamma in the mPFC increases from ~80 Hz to ~100 Hz as faster breathing occurs when rats experience anxiety[60]. In addition to frequency–frequency correlations, the breathing rate in mice also relates to the level of theta–gamma coupling during rapid eye movement sleep[40]. This relationship follows an inverted V-shaped dependence, with maximal theta–gamma coupling occurring at intermediate breathing rates of 4–6 Hz[40]. These new results indicate that breathing and the brain interact in far more complex ways than phase-based modulations during individual breathing cycles.

Origins of respiratory brain synchrony

We have so far described a wide range of neuronal activities with synchrony to the breathing cycle, which we dub 'breathing–brain signals'. What are the mechanisms linking breathing and brain activity? A myriad

Fig. 2 | Candidate sources and neural pathways for breathing–brain signals. **a**, In mammals, multiple processes are causally or flexibly coupled to the phase of the breathing oscillator. As the diaphragm contracts, the lung expands, bringing O_2-rich air into the lungs via ingoing airflow in the nose. As inhalation progresses, the heart rate and baseline arterial pressure increase, to varying degrees, through respiratory–cardiovascular coupling. The emission of vocalizations is locked to exhalations. Body movements can flexibly synchronize with breathing, from postural changes to accommodate chest inflation to different modes of aligning strides with respiratory cycles during locomotion. In some mammals, such as rodents, exploratory behaviour brings about a global synchrony of orofacial rhythms to breathing, with whisker and head protractions in phase with inhalations. All of these processes could, in principle, contribute to modulating brain activity in synchrony with the breathing rhythm. **b**, Neural pathways by which these processes might modulate brain activity through the broadcasting of motor commands and/or sensory activity (interoceptive or exteroceptive). Only selected areas and connections are shown; note that some connections are depicted based on evidence from non-human mammalian species. Dashed lines represent pathways for which the experimental support for propagating breathing–brain signals is weaker. Neurons in the pre-Bötzinger complex (preBötC) of the breathing central pattern generator (CPG) orchestrate rhythmic inhalation by driving diaphragm motoneurons, and also directly project to the respiratory nucleus of the solitary tract (NTS) and parabrachial nucleus (PBN) in the brainstem and to the thalamus[115]. Through these relays, it is hypothesized that copies of the breathing motor programme (corollary discharges) could reach forebrain targets including the amygdala (AMY), horizontal limb of the diagonal band of Broca (HLDB), olfactory bulb (OB) and thalamus[23,125,128,129]. preBötC neurons further target the locus coeruleus (LC), which provides broad noradrenergic modulation to the forebrain[116,117]. The diaphragm motor cortex commands the breathing pattern during voluntary inhalation in humans and, in so doing, gives rise to a cortical breathing–brain signal of its own[104,105]. Breathing interoception from pulmonary and diaphragm stretch receptors enters the brain through parallel pathways: lung and/or airway afferents target the NTS through the vagus nerve[154,155], from which the lung-inflation rhythm could propagate through pathways partially shared with the putative corollary discharges mentioned above, whereas diaphragm mechanosensors target the somatosensory thalamus through the phrenic nerve, through which diaphragm contraction cycles drive activity in specific areas of the somatosensory cortex (SC)[161–164]. Interoceptive respiratory modulation of brain activity could further emerge from pulsations in intracranial pressure (ICP), secondary to the fluctuations in cerebral arterial pressure that are coupled to the breathing cycle[146,150,152]. Exteroceptive respiratory-coupled sensory activity involves mainly the olfactory and somatosensory systems. Body touch and proprioception would be expected to track the breathing rhythm only when movements are overtly synchronized to it. Airflow recruits neurons encoding touch and thermoception in the respiratory epithelium of the nasal cavity, which probably drive specific targets in the somatosensory thalamus and cortex at the breathing rhythm[175,176,178,195]. Olfactory sensory neurons in the olfactory epithelium are mechanically and chemically activated by the cyclic flow of air and odorants through the nasal cavity. Through the OB, anterior olfactory nucleus (AON) and piriform cortex, this respiratory-coupled activity spreads across cortical and subcortical structures, including the entorhinal and prefrontal cortices[29,30,188], AMY[185], HLDB[270] and hippocampus (HC)[186,187]. **c**, Activation of the olfactory epithelium by nasal airflow is a potent driver for distributed breathing–brain signals and, so far, the only experimentally confirmed source of these signals in areas above the thalamus[5,18,19,26,28–30,34,43]. During normal breathing (left), air flows cyclically in and out of the nose, and brain local field potentials (LFPs) exhibit an oscillation synchronous to it, which can coexist with other endogenous neuronal oscillations, such as theta oscillation. Diverting airflow from the nose through a tracheostomy (middle) abolishes the breathing–brain signal, while sparing endogenous oscillations. In turn, imposing artificial rhythmic airflow in the nose through air puffing (right) elicits a brain rhythm at the puffing frequency. Illustrations are schematic representations of the findings from refs. 26,28.

of sensory, motor and physiological processes have been shown to be either constantly or flexibly synchronized to the breathing rhythm (Fig. 2a). Given that these processes are inevitably linked to neuronal activity in some specific part of the CNS, this activity will probably show synchrony with the breathing cycle (Fig. 2b). Physiological variables, such as blood oxygenation, pH and pressure, which are also affected by breathing, can modulate neuronal activity as well, but may not do it fast enough to synchronize it to the breathing rhythm. Does the observed brain synchrony to breathing emerge from the concerted action of all of these sources, or does the evidence point to one of them as the main driver?

Most candidate sources of breathing–brain signals are causally related — for example, the motor commands that contract the diaphragm expand the lungs and chest, which brings air and odorants in through the nostrils. Therefore, correlations alone cannot determine the origin of a given brain–breathing signal; anything showing synchrony with one candidate will typically be in sync with all the others. Manipulations that decouple one candidate source from the rest are thus needed.

For a particular brain signal with respiratory synchrony, its true source should fulfil several criteria. First, it must be synchronous to the respiratory cycle (synchrony condition; mere correlation with the breathing rate does not qualify). Second, there must be a plausible route from the source to the neurons driving the brain signal (whether synaptically or by diffuse tissue action) that is fast enough to reflect changes in breathing within a few hundred milliseconds and responsive enough to modulate neuronal activity on a cycle by cycle basis (plausibility condition). Third, experimentally decoupling the candidate source from breathing must eliminate or substantially reduce the respiratory synchrony of the brain signal (necessity condition). Last, artificially driving the source with a pattern independent of ongoing breathing must impose that pattern on the brain signal (sufficiency condition). We will next examine the main candidates and assess our current knowledge on how well they meet these criteria.

Motor activity

Skeletal muscle contractions directly reflect the activity of specific motor neurons in the brain or spinal cord, and typically also depend on more widespread activation of neurons in motor and premotor areas across the brain. If muscle contraction is synchronous with breathing, it is likely that the neuronal activity across the motor neuraxis will also be synchronized and will, by definition, constitute a breathing–brain signal.

The most salient motor activity that is in synchrony with breathing is, of course, breathing itself. In mammals, inspiratory pump muscles are recruited during the active inhalation phase of breathing, which (depending on the regime) can be followed by activation of laryngeal adductors during post-inspiration and/or expiratory muscles during active exhalation[103]. This alternating sequence of muscle activations is generated by the brainstem breathing central pattern generator (CPG) (Fig. 2b) network, within which the pre-Bötzinger complex (preBötC) functions as the pacemaker by commanding inspirations[103]. In humans, the motor cortex can bypass the CPG to control the diaphragm during voluntary inspirations[104,105] (Fig. 2b). Additional motor programmes

that synchronize with breathing more flexibly include those mediating postural control, locomotion[106] and, in many non-human mammals, orofacial activities such as whisking and nose and head movements[107,108] (Fig. 2a).

Motor signals can spread outside their principal neuraxis through corollary discharges, in which copies of motor activity are sent to other non-motor areas. Corollary discharges allow animals to match sensory inputs to the context of their own actions[109,110] and are particularly prevalent in active sensing systems — such as electric sensing in fish and gaze-assisted vision in primates[111,112] — where they help circuits to dissect sensory inputs caused by external sources from those caused by the animal's own actions. As breathing is the active driver for olfaction[113,114], corollary discharges from the respiratory motor neuraxis are natural candidates for mediating the breathing rhythmicity found across olfactory areas and beyond.

Excitatory and inhibitory neurons in the mouse preBötC project to a widespread set of nuclei in the brainstem and diencephalon[115] (Fig. 2b). However, there are no known monosynaptic connections from the breathing CPG that could directly drive the respiratory brain signals found across the telencephalon. Some indirect pathways can be traced, but none have been functionally confirmed. For a given nucleus to be considered as a putative relay for respiratory corollary discharges, it must receive afferent connections from the breathing CPG and exhibit neuronal activity aligned to the breathing cycle. Currently, pathways through the locus coeruleus (LC), parabrachial nucleus (PBN) and thalamus stand out as candidates (Fig. 2b).

The LC is the sole source of noradrenergic modulation across the forebrain, targeting virtually all brain regions and having roles in vigilance, attention, sensory processing and memory[116,117]. In rodents, the LC receives direct inputs from a subpopulation of preBötC neurons, providing a possible pathway for the regulation of arousal and other brain processes by breathing[115,118]. Neurons in the LC have been shown to fire in synchrony with respiratory muscle activity[119,120] and phasic activation of the LC can be followed by transient increases of gamma activity in the mPFC, a known LC target[121,122]. The LC also sends extensive projections to the rodent OB, where olfactory gamma bursts are prominent[123]. Although there is no direct evidence that LC activity drives forebrain breathing signals, its potential involvement in the respiratory modulation of frontal gamma oscillations could explain why the power of breathing-driven gamma is dramatically diminished during sleep[67,71], coinciding with greatly reduced noradrenergic output from the LC[116].

The PBN lies at the circuit cross-roads between ascending interoception and descending autonomic control[124]. Projections from the preBötC reach the rodent PBN directly or indirectly through the respiratory division of the nucleus of the solitary tract (NTS) in the medulla[115,125]. Neurons firing in synchrony with breathing can be readily found throughout the NTS and PBN of cats[126,127]. Forebrain targets of the PBN include areas with known respiratory synchrony, such as the AMY, thalamus and basal forebrain[23,125,128,129]. The horizontal limb of the diagonal band of Broca (HLDB) in the basal forebrain could relay breathing corollary discharges to the limbic system through its dense cholinergic and GABAergic innervation of the OB and olfactory cortex[130–132].

Thalamic nuclei also receive direct projections from the preBötC, and respiratory modulation of neuronal firing has been described in the thalamus and subthalamic nucleus of rodents, cats and humans[5,43,54,133,134]. Interestingly, thalamic neuronal firing synchronized with central respiratory activity persists in experimental conditions that eliminate most respiratory sensory feedback and is abolished when the brain is transected below the midbrain[134], suggesting that it could indeed reflect efferent drive from the respiratory CPG. Considering the dense and bidirectional nature of thalamocortical connectivity, this ascending pathway could, in principle, broadcast a copy of the respiratory motor programme across the neocortex, whereas the AMY and basal forebrain could relay it throughout the limbic system.

Circuits in the brainstem and diencephalon are notoriously complex, with each nucleus typically comprising subnuclei that can harbour overlapping neuronal populations with distinct neurochemistry and connectivity. Given the current lack of detail on the specific location, molecular identity and connectivity of the respiratory-modulated neurons described above, it is impossible to assert that they indeed broadcast respiratory corollary discharges to the forebrain. Thus, although breathing corollary discharges are plausible, there is as yet no evidence for their necessity or sufficiency in rhythmically driving the brain.

Interoception

Sensory systems are typically categorized as interoceptive — providing information about the internal state of the body — or exteroceptive — sensing the external world[135–137]; however, the line between these is sometimes hard to draw. Several physiological variables related to the cardiovascular system synchronize with the respiratory cycle and could therefore act as interoceptive signals to modulate forebrain neuronal activity.

O_2 and CO_2 concentrations. Each breathing cycle exchanges CO_2-rich air in the lung alveoli with O_2-rich external air. However, because only a fraction of the pulmonary air is replaced and normal alveolar oxygen pressure (PO_2) remains at almost saturating values for haemoglobin, the arterial oxygen content remains largely constant across inspirations and expirations[138]. Subtle modulations in PO_2 within cerebral arteries during the breathing cycle have been described in cats and mice[139,140], although it is unclear whether these fluctuations are sensed by brain cells. Furthermore, even in small mammals, arterial changes in PO_2 lag those in the lung by more than a second[139]. Overall, although cerebral oxygenation levels can influence brain function[141], cycle by cycle respiratory modulation of brain tissue oxygenation appears unlikely to account for breathing–brain signals, which immediately follow breathing changes. A similar case can be made for CO_2: although carbon dioxide pressure (PCO_2) levels can have sizeable effects on neuronal function through changes in tissue pH[142], arterial PCO_2 is not expected to fluctuate much within each breathing cycle, and any local effects in the brain would lag ongoing breathing by seconds.

Outside the brain, arterial chemoreceptors that sense PO_2, PCO_2 and pH convey ascending signals to the NTS via the glossopharyngeal and vagus cranial nerves[138]. However, even if these receptors could track marginal fluctuations in PO_2 and/or PCO_2 within breathing cycles, they would not be expected to contribute to breathing–brain synchrony under physiological conditions, as they are selectively engaged by abnormal blood content[143].

Intracranial pressure. Intracranial pressure (ICP) exhibits pulsatile components in both the heart and the breathing rate in many species, including humans[144–148]. These pulsations drive cerebrospinal fluid flow[147] and reflect both the acute rises in arterial pressure created by heartbeats and the slower modulation in systemic blood pressure caused by the respiratory rhythm. The heart rate itself can

be modulated by the breathing phase, rising during inhalations and decreasing during exhalations, such that ongoing breathing also affects ICP through changes in the instantaneous rate of cardiac pressure pulses[149]. Principal neurons from widespread brain areas can be directly activated by pressure stimuli in ex vivo preparations, possibly through the opening of PIEZO2 mechanosensitive cationic channels[150–152]. The blood pressure in brain arterioles could also indirectly modulate neuronal activity via specialized perivascular astrocytes, but this pathway is likely to be too slow to efficiently entrain neurons at the respiratory rhythm[153]. Interventions to specifically decouple ICP from the breathing rhythm are needed to test the possibility that ICP has a role in globally driving respiratory brain signals.

Lung mechanotransduction. Mechanical sensation from the lungs warrants special consideration. Pulmonary stretch receptors with mechanoreceptive nerve endings within the smooth muscles surrounding the airways project centrally via the vagus nerve[154,155]. Because they are selectively active during inspirations, when the lungs inflate, respiratory rhythmicity is readily apparent in vagal nerve spiking[156–158]. Although the role of this phasic activity during normal breathing remains unclear, pulmonary stretch receptors become increasingly engaged with deeper breaths, triggering a reflexive shortening of inhalations[138,155]. Through the respiratory NTS, pulmonary stretch receptor activity reaches the PBN[154], which is well positioned to distribute it centrally (Fig. 2b). Consistent with this idea, electrical vagal stimulation can modulate the activity of neurons across forebrain areas in rats and monkeys[159,160].

A parallel set of mechanical interoceptors provide fast feedback on diaphragm stretch and contraction: muscle spindles and Golgi tendon organs, which activate during the expiratory and respiratory phases, respectively[161]. Their large myelinated fibres travel via the spinal phrenic nerve to the somatosensory thalamus[161,162] (Fig. 2b). Mechanical and electrical activation of these mechanoreceptors evokes short-latency neuronal activity in the somatosensory thalamus and cortex, contributing to the conscious perception of breathing[162–164].

Although mechanical feedback from the airways stands out as an interesting candidate source of breathing–brain signals, we are not aware of any evidence that vagal or phrenic interoception is required for the expression of such signals above the brainstem. A reasonable prediction would be that any signal conveyed by these interoceptors should be enhanced when the lung tidal volume is expanded, such as during heavy exercise[165] or hypercapnia[166].

Exteroception

Classical exteroceptive systems can sense our breathing: through touch we feel our chest expanding and air moving into the nose; through olfaction we feel the odours brought in by inspirations; and even vision and audition can pick up subtle breathing-locked stimuli. Current evidence points to nasal airflow as the most likely candidate to mediate widespread breathing–brain synchrony.

Nasal airflow and olfaction. It has long been established that the breathing signals prevalent across the early stages of odour processing have a nasal origin[3]. From the very discovery of breathing-related modulations in the olfactory system[8], researchers have used tracheotomy to determine whether they result from nasal airflow or reflect efferent activations from central respiratory centres. Diverting natural breathing away from the nose (via tracheotomy or mouth breathing) and then imposing artificial flow patterns through it have consistently proven that nasal airflow is necessary and sufficient to modulate the primary olfactory system at the (nasal) breathing rate across species[8,26,28,30,34,44,49,167–171], and the extent of this modulation depends on airflow properties[172,173]. This may come as little surprise, considering that inhalations time the exposure of olfactory sensory neurons in the olfactory epithelium to their preferred odorants. However, it has been shown that the inspiratory flow of 'clean' (non-odorized) air is also sufficient to drive 'olfactory' circuits[174], suggesting that mechanosensation could be involved.

Somatosensory fibres from the trigeminal nerve that convey touch, temperature and chemical sensations from the nasal mucosa[175] (Fig. 2b) show robust synchrony to breathing[176] and mediate the feeling of nasal airflow[177,178]. Thus, interrupting or imposing nasal airflow would (in addition to affecting olfaction) block or recruit nasal somatosensation, which could modulate the OB through direct or indirect pathways[175,179]. However, the effect of chemical ablation of the olfactory epithelium, which is believed to spare nasal cavity somatosensation[180], is comparable with that of abolishing nasal airflow in impairing the respiratory synchrony of the OB in rodents[30,67]. Furthermore, in one study, olfactory cortex responses to inhalation were not affected by sectioning one of the trigeminal branches that innervate the nasal mucosa[181] (but note that other branches with known respiratory modulation[176] were not severed). This supports a role for direct mechanical stimulation of the olfactory sensory neurons themselves in the generation of breathing–brain signals. Indeed, these neurons respond not only to odorant binding but also to mechanical (pressure) stimuli[182], with both mechanosensitivity and chemosensitivity being mediated by the same membrane receptors[182,183].

Given these findings, researchers have asked whether nasal airflow also contributes to the breathing–brain signals more recently detected in non-olfactory regions. Diverting airflow away from the nose or disrupting the olfactory pathway almost entirely abolishes the breathing modulation of the LFP across the HC[26,28,34,43], AMY[34] and prefrontal[5,19,29,30] and somatosensory[18] cortices (Fig. 2c). In turn, artificially activating the nasal epithelium with airflow or stimulating the olfactory circuits evokes time-locked responses in the LFP of the HC[26,28,184] and prefrontal[30] and somatosensory[18] cortices (Fig. 2c). This extensive propagation is anatomically plausible, given that the OB targets most of these regions, reaching the amygdaloid complex monosynaptically[185], the HC through the entorhinal cortex[186,187] and the mPFC via primary olfactory cortices and the anterior olfactory nucleus (AON)[29,30,188] (Fig. 2b). Cyclical activation of the olfactory epithelium by the alternating influx and efflux of air and odorants in the nose thus fulfils all four conditions for a source of breathing–brain signals: synchrony, plausibility, necessity and sufficiency.

Somatosensation. Although less well studied, one would expect somatosensory inputs outside the nasal cavity to contribute to breathing–brain signals, at least within their specific termination areas in the thalamus and cortex[35,51,189–191] (Fig. 2b). Arguably, these signals would be enhanced when more of the body couples with the respiratory rhythm (for example, during active behaviours in rodents in which the head, nose, whiskers and vocalizations all act in concert with the diaphragm[107,108,192,193], or during locomotion when strides can synchronize the whole body to breathing[106,194]) (Fig. 2a). Neuronal activity in a recently discovered primary sensory cortex area for nasal touch in rodents shows marked respiratory synchrony[195], but more work is needed to assess the depth and spread of breathing somatosensory signals across the brain.

An overall mechanistic view

Current evidence suggests that nasal airflow, through the rhythmic activation of the olfactory neuraxis, is a powerful driver of the distributed breathing synchrony observed in the mammalian cerebrum — and the only confirmed one to date. Given that olfaction is usually conceptualized as exteroception, how should we think about its mechanosensitive component, which is unlikely to have evolved to sense variations in external atmospheric pressure. Its functions may lie closer to those of interoception, whereby the nasal breathing rate and depth signal internal states, or corollary discharges, with the nasal breathing phase serving as a reference for active olfactory sampling. For whisking (a similarly rhythmic active sense), a possible corollary discharge has been described in the barrel cortex; however, it does not follow the whisking rhythm[189], suggesting that any whisking phase coding must rely on the afferent periodic signal as a reference. Although odour exposure can increase the respiratory modulation of olfactory neurons, little is known about how odours affect breathing signals elsewhere in the brain. An interesting possibility is that chemosensory and mechanosensory components of olfactory neuron activity are differentially propagated beyond the olfactory system, paralleling recent observations for rhythmic whisking signals[196].

Most of the respiratory signals for which there is strong evidence of a nasal origin were recorded from brain areas that lie within or are closely associated with the limbic system, a network of structures with patent links to olfaction[197–199]. Furthermore, outside the olfactory system, the effect of blocking nasal airflow or the olfactory pathway has been assessed almost exclusively for LFP signals. Not all neuronal activations will produce voltage changes detectable by LFP electrodes[55]. For individual neurons, a few studies have reported respiratory synchrony even under tracheostomy in the rat OB[200], and in cat thalamic and subthalamic nuclei[133,134], whereas one study showed that ablation of the olfactory epithelium considerably reduced — but did not eliminate — the breathing modulation of neurons in the mouse mPFC, HC and thalamus[5]. If confirmed, these results could reflect distributed coupling of neurons to the breathing rhythm via non-nasal pathways; activations that perhaps do not sum to produce detectable LFP signals. Overall, although more research is needed to directly gauge the possible contributions of ICP, ascending interoception or corollary discharges, anyone attempting to attribute the source of a brain signal locked to the respiratory cycle would be wise to first discard a nasal or olfactory origin.

Breathing–brain signals are independent from endogenous slow oscillations. What are the mechanisms by which nasal airflow generates breathing–brain synchrony? One important question is whether the respiratory synchrony observed across the brain reflects the phase-locking of endogenous neuronal oscillations — such as delta and theta — to the breathing rhythm through a phenomenon known as entrainment, or emerges from the sequence of sensory evoked potentials triggered by each cycle of nasal airflow, independent of any ongoing endogenous oscillation.

Entrainment occurs when two oscillators, which could follow different frequencies when isolated (their 'natural' frequencies), become synchronized through unidirectional or bidirectional coupling[201–203]. It is worth noting that we and others have previously used the term 'entrainment' in a broader sense, not necessarily implying the synchronization of an autonomous brain oscillation by an external agent[204]. Determining whether a periodic sensory input entrains or evokes brain activity can be challenging, as both mechanisms produce activity that is frequency-locked to the rhythm of the inputs[204]. In cases of entrainment, there should be evidence that a brain oscillation exists without the rhythmic stimulations, whose frequency shifts to that of the input during stimulation. Furthermore, only brain rhythms with frequencies close to the rate of the sensory inputs are reasonable candidates for entrainment, as such coupling becomes progressively harder as the difference in natural frequencies increases[201].

Although this issue has not been explored in humans, rodent LFP recordings provide substantial evidence against the suggestion that the breathing rhythm entrains endogenous oscillations. Brain activity can synchronize with rodent breathing at all rates[59] — from 1 Hz to 12 Hz — and no endogenous oscillation is known to span this frequency range. Thus, breathing would need to 'jump' between entraining delta or theta oscillations, depending on its rate. Moreover, respiratory LFP rhythmicity can coexist and be clearly distinguished from ongoing delta and theta oscillations[6,26–28] (Fig. 2c). In the HC, it was shown that breathing-coupled LFP oscillations differ from the theta oscillations (6–10 Hz) that are prominent in this area[26–28] and that the two rhythms may simultaneously occur. The peak frequency of the LFP breathing rhythm can be below, within or above the theta-frequency range depending on the breathing rate[6,27]. Consistent with these observations, blocking nasal inputs selectively abolishes the breathing oscillation in the HC and mPFC while sparing theta oscillations[26,29], whereas a muscarinic antagonist[205] eliminates hippocampal theta under urethane anaesthesia while sparing the local respiratory LFP rhythm[26]. The breathing-coupled LFP oscillations were also proven distinct from other slow oscillations in the delta-frequency range seen during slow-wave sleep and anaesthesia, although they could also coexist with such oscillations[28]. We therefore conclude that nasal breathing does not modulate rodent brain activity by entraining local delta or theta oscillations.

Further evidence against entrainment is provided by the observation that respiratory LFP components in the OB and mPFC occur with constant latency to inhalations across breathing rates[22,59,206]. This is expected for sensory evoked potentials with fixed transmission time delays, but is incompatible with models of neuronal entrainment, which predict that brain oscillations should follow sensory inputs with a fixed phase relationship across rates[207]. The breathing–brain rhythms — or, at the very least, those in rodent LFP signals — should thus be considered independent oscillations imposed by sensory inputs. As such, their functions cannot be directly inferred from those of other well-studied endogenous neuronal oscillations.

Functions of breathing–brain interactions

Through its effects across the brain, breathing influences several functional processes[2,208,209], a likely evolutionary adaptation (Box 3). Evidence indicates that breathing can affect brain function by pacing the formation of cell assemblies and the occurrence of faster endogenous network oscillations, and by providing a common reference signal that coordinates neuronal activity underlying sensory, motor and cognitive processes.

The concept of the cell assembly has long been considered fundamental to brain operation[85]. Breathing-evoked potentials permeate brain networks and coordinate firing among neurons; as a result of this, coupling between breathing and gamma rhythms emerges[66]. Mechanistically, gamma oscillations arise due to a rhythmic interplay between inhibitory interneurons and large cohorts of principal cells[84]. During a transient bout of breathing-nested gamma activity, the principal neurons that activate the most recruit inhibitory interneurons

Box 3 | An evolutionary perspective on breathing–brain interactions

Mammalian olfaction evolved to be intricately linked to the rhythm of breathing, making it an intrinsic feature of odour coding and, over time, other brain processes. Although the strong grip of the olfactory circuit on the brain may seem surprising from our anthropocentric perspective, we should bear in mind that the olfactory system was relatively massive, compared with other brain regions, when mammals first emerged[275] and is considered a fundamental driving force behind the evolution of our forebrains, including early cortical expansions[276]. The mammalian brain, therefore, probably evolved under a constant barrage of activity stemming from the nose, which can reasonably be assumed to have oscillated at the breathing rhythm throughout this evolutionary history.

What was the adaptive value of tying several brain functions to breathing? One likely explanation lies in the benefits of the discontinuous nature of breathing[113,277]. Continuous stimulation often leads to adaptation and habituation, which enhance novelty detection but reduce sensory sensitivity. Rhythmic interruptions, as provided by breathing, prevent this habituation and help to maintain sensory responsiveness[277]. Many biological systems capitalize on interruptions[277]: vision relies on saccades to refresh the visual scene, tactile perception benefits from discontinuous textures such as those in Braille, and memory and navigation processes use theta and gamma rhythms for cyclic interruptions of neuronal activity. Even arthropods, such as insects and crustaceans, which detect odours through their antennae without breathing interruptions, engage in rhythmic movements — often referred to as 'sniffing'[278] — when tracking scents, mimicking the role of breathing oscillations in mammals.

Beyond olfaction, the brain may have leveraged the intermittent nature of breathing to structure additional neural computations (an idea originally proposed in ref. 63). As brain complexity increased, these oscillatory rhythms were probably co-opted — or 'hijacked' — to support broader functions[63,279], an evolutionary repurposing that conserved neural resources. By providing temporal scaffolding, breathing rhythms may facilitate cell assembly formation, interregional communication, synaptic plasticity and learning, balancing sustained neural activation with periods of relative quiescence to optimize sensory and cognitive functions. Thus, breathing rhythms have been adopted by various brain systems as an evolutionary exaptation. In humans, the ability to consciously control breathing has further extended this adaptation, allowing for intentional modulation of emotions and global brain states. This unique capacity illustrates how ancient olfactory rhythms evolved to serve complex functions in higher-order cognition. Understanding this transition offers a glimpse into the evolutionary pressures shaping neural circuit organization and underscores the central role of breathing in linking sensory, motor, emotional and cognitive processes.

which, in turn, suppress competing neurons, creating a winner-take-all dynamic that influences cell assembly membership[66,86].

Across the brain, neuronal activity is often timed relative to external inputs or internal brain rhythms. This results in the encoding of information in the precise timing of spikes (temporal coding) rather than the spike rate. In particular, the phase of a neuronal spike relative to ongoing brain oscillations encodes information about external stimuli or internal states[210–212]. Therefore, the phase of the breathing-coupled oscillation may serve as a temporal framework for coordinating neuronal activity. Evidence for this comes from a study showing that mice can distinguish the breathing phase in which olfactory sensory neurons were stimulated[213]. In the following subsections, we will further explore how breathing influences brain function.

Olfactory coding

Breathing patterns associated with olfactory sampling, known as sniffing (typically >4 Hz in rodents), function as active sensing mechanisms[15,107,113,214–216]. Animals synchronize whisker, nose and head movements with the breathing cycle to navigate the odour landscape[107,217,218] (Fig. 2a), with the preBötC proposed as the master clock coordinating these orofacial rhythms[219]. This coordination is particularly evident during goal-directed behaviours and diminishes when task demands are absent[220].

A single sniff can suffice for accurate odour discrimination in animals and humans[221–225], indicating that the necessary computations for odour perception can occur within one respiratory cycle[15,113]. Olfactory circuits are therefore optimized to process information rhythmically and in synchrony with the breathing cycle[113]. Indeed, in slice preparations of the rodent OB and olfactory cortex, where processing is decoupled from sampling, mimicking breathing patterns using rhythmic electrical stimulation enhances neuronal responses, gamma oscillations and information integration[226–228].

Recent evidence has shown that animals must encode the physical properties of the breathing cycle to distinguish between changes in odour concentration and airflow[181,229]. Faster sniffs move more air and odorants through the nose, activating more olfactory receptors and mimicking higher odorant concentrations[230]. To separate these effects, particularly when locating an odour source, olfactory sensory neurons also detect air pressure and relay this information downstream, allowing independent representations of concentration and airflow speed in the olfactory cortex[174,181,182].

In rodents, the breathing phase has been shown to precisely coordinate firing patterns within the olfactory system, with distinct neurons and cell–odour pairs exhibiting specific 'firing fields' that tile the entire breathing cycle[94,113,213,231]. This mirrors other examples of variables encoded by oscillatory brain activity, such as the encoding of spatial location by theta-nested place cell sequences in the HC[210]. This parallel suggests that odour identity may be similarly encoded by the phase of firing within the cycle[167,232,233] (Fig. 3a). Moreover, spike timing relative to the breathing cycle enables the segregation of distinct coding streams[167,234–236]. For instance, odour identity is best decoded at the beginning of the cycle, whereas concentration decoding occurs later[236]. Theoretical and experimental evidence further suggests that the concentration is encoded by the relative timing within the breathing cycle, as higher concentrations activate the olfactory glomeruli earlier[233–236].

The breathing phase code may be particularly relevant in the olfactory cortex, where odour-encoding ensembles are sparsely distributed along the antero-posterior axis[237,238], and would benefit from a shared

reference signal for synchronization. Supporting this, the breathing phase has been shown to modulate communication between the mouse OB and olfactory cortex and to organize feedforward and feedback interactions[94]. Moreover, both olfactory perception in humans and odorant decoding in mice correlate with breathing-driven gamma oscillations in the olfactory cortex[50,66].

Fear responses and emotional regulation

The functional role of breathing also influences processes further along limbic system pathways, where breathing-coupled oscillations regulate emotions and fear-related behaviours. In rodents, OB removal leads to severe behavioural changes resembling major depression[239]. Recent findings suggest that these emotional disturbances are linked

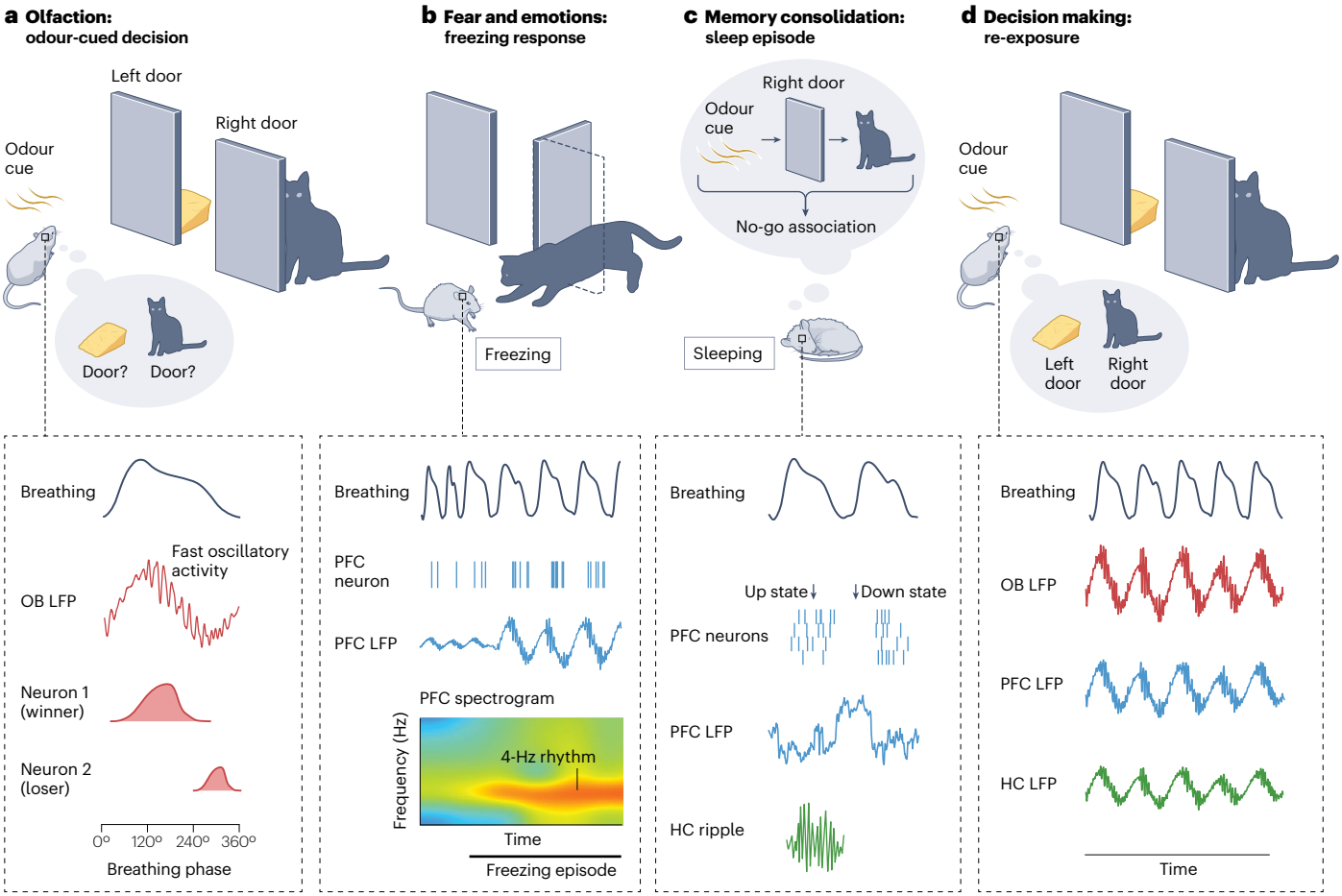


Fig. 3 | Influences of breathing on brain function. Some functional outcomes of respiratory modulation of neural activity in brain regions involved in sensory processing, emotional regulation and higher cognitive functions. These examples represent a hypothetical scenario and the likely influence of breathing at each stage, with schematic representations of possible neural activity based on published results[2,7,19,30,31,66,88,232,236,243,253]. **a**, The effect of breathing on olfactory encoding. During its first exposure to an odour-cued decision, a rat must choose between two doors, based on an odour cue. Behind the doors, there is either a reward (cheese) or a dangerous threat (a cat). During the odour sampling period, inhalation-driven nasal airflow generates oscillatory local field potential (LFP) activity in the olfactory bulb (OB) and neuronal phase-locking, with distinct neurons showing different preferences for firing within particular breathing phases[232]. The most rapidly activated neurons (Neuron 1, in this example) spike earliest within the breathing cycle and inhibit others (Neuron 2) by recruiting local interneurons, which gives rise to a transient fast network oscillation detectable in the LFP recordings[66]. This results in a winner-take-all process and ensures that odour identity is encoded by 'winner' neurons that fire during the early phases of the breathing cycle and suppress 'loser' neurons[66]. **b**, Breathing influences fear and emotions. If the rat chooses the wrong door, it is exposed to a threatening stimulus and freezes. During freezing, medial prefrontal cortex (mPFC) assemblies and LFP oscillations strongly synchronize with breathing, resulting in a prominent 4 Hz rhythm on the spectrogram (a temporal representation of the frequencies present in the LFP)[19,30,88,243]. This breathing-coupled rhythm has been directly linked to the maintenance of the freezing response during fear behaviour[19]. **c**, Memory consolidation has also been suggested to be regulated by breathing. In rodents, during post-experience sleep, the breathing phase influences the transition between up and down states in the cortex and the timing of ripples in the hippocampus (HC), which are required for long-term memory consolidation[5]. As a result, animals consolidate the memory trace. In this case, the memory of choosing the wrong door, based on an odour cue, and encountering a life-threatening situation is consolidated, probably establishing a no-go association in prefrontal cortex (PFC) decision-making neurons. **d**, Breathing also affects decision-making. As the animal begins another trial in the same task, breathing again influences neural dynamics across the OB, PFC and HC to guide adaptive behavioural outcomes[7,253]. Consequently, the rat harnesses breathing-aided communication to avoid the threatening door and secure the cheese reward.

to the disruption of OB-derived limbic gamma oscillations[240]. Indeed, bulbectomy-like symptoms can be induced by perturbing olfactory gamma oscillations, whereas reinstating these oscillations alleviates the symptoms[240]. These results underscore the crucial role of nasal breathing-driven gamma oscillations[65,67,241] in regulating limbic circuits and mood.

Breathing also regulates fear-related behaviour. Freezing, a defensive response to threat, involves the synchronization of neuronal activity between the mPFC and the basolateral AMY[242]. Studies in mice demonstrated that a 4 Hz oscillation dominates PFC activity during freezing and synchronizes prefrontal–AMY circuits[88,243]. Subsequent research revealed that this 4 Hz oscillation corresponds to the breathing-coupled LFP rhythm, which emerges in limbic circuits during fear responses[5,19,30] (Fig. 3b). Optogenetic induction of the 4 Hz rhythm in the mPFC through modulation of interneuron activity increases co-firing between the mPFC and AMY neurons and elicits freezing behaviour[243]; conversely, disrupting breathing-related signals reduces freezing maintenance[19]. Moreover, the phase of the breathing cycle coordinates the neuronal activity underlying fear responses: optogenetic inhibition of prefrontal assemblies during the ascending 4 Hz phase blocks freezing, whereas inhibition during the descending phase prolongs it[88]. In rats, coupling between mPFC LFPs and breathing has also been observed during freezing[244] and anxiety-like behaviours[60], and it is possible that the slower type 2 theta oscillations seen in limbic structures during immobility in response to a predator stimulus[245,246] also correspond to breathing-coupled oscillations. In all, these findings show how internalized bodily rhythms can orchestrate emotion-related behaviours.

In humans, recognition of emotional facial expressions occurs faster during nasal than oral breathing, with nasal breathers showing a tendency for quicker detection of fearful expressions during inspiration compared with expiration[34]. Beyond facial recognition, breathing has a broader role in the regulation of emotional states in humans. Breathing patterns shift in response to different emotions[247]. Interestingly, breathing not only reacts to emotions but can also actively influence them, with changes in respiratory patterns altering emotional experience, even without conscious awareness[248]. For instance, slow, controlled breathing can reduce anxiety and promote relaxation[249,250], a technique thought to work by modulating limbic circuits[251,252]. Supporting this possibility, intracranial studies in humans have shown that nasal respiration drives oscillatory activity in the limbic system[34,35]. Although further research is needed to fully understand how breathing influences emotional processing in humans, the rhythmic modulation of brain circuits may represent a key physiological mechanism.

Memory

Breathing also influences short and long-term memory (Fig. 3c). The effect of breathing on working memory was initially studied unknowingly in rats, in which a 4 Hz rhythm — now recognized as corresponding to breathing-coupled oscillations[5,30] — was shown to emerge in the mPFC and ventral tegmental area in an odour-cued spatial decision task[253]. This rhythm coordinated neuronal activity across the mPFC, ventral tegmental area and HC, with a notable increase in its power and coherence during stages of the task that placed demands on working memory. The phase of the 4 Hz rhythm modulated both gamma activity and neuronal spikes; importantly, mPFC neurons that predicted task choices were more strongly modulated than non-predicting neurons. Similar results were recently reported by an independent study that included nasal breathing recordings[7]. A coherent breathing-coupled rhythm occurred in the rat OB, mPFC and hippocampal CA1 areas in an analogous odour-cued decision-making task and modulated faster beta oscillations associated with odour processing and the spiking of task-responsive cells[7]. Thus, breathing-coupled oscillations have an important role in working memory processes by coordinating activity across engaged brain regions (Fig. 3d).

The rodent literature also provides substantial indirect evidence that breathing modulates other memory-related brain processes. Breathing has been shown to modulate key areas implicated in memory formation and consolidation, including the HC, AMY and neocortical regions[5,6], and to organize neuronal activity patterns and cross-regional interactions previously linked to memory functions[5,31]. In particular, during offline states such as slow-wave sleep — when animals are disengaged from the external world and the transfer of memories from the HC to the neocortex is thought to occur — the breathing phase coordinates transitions between neocortical up and down states and hippocampal SWRs, a physiological substrate of memory replay and consolidation[254] (Fig. 3c). It has been hypothesized that the phase-locking to breathing ensures temporal alignment between hippocampal SWRs and neocortical excitability, thus optimizing memory transfer[2]. This supports the suggestion that breathing has a pivotal role in orchestrating the network dynamics necessary for memory consolidation[5].

The influence of breathing (or the related olfactory input) on memory processes has also been investigated in humans. Notably, presenting familiar odours encountered during learning while participants were in slow-wave sleep significantly improved the retention of HC-dependent declarative memories[255]. This effect did not occur during rapid eye movement sleep or wakefulness[255], suggesting that olfactory cues enhance memory consolidation in a state-dependent manner. Similarly, odour presentation during sleep increased slow-wave and spindle activity in the EEG recording[256]. Although these experiments cannot distinguish between the effects of olfactory input and those of breathing, recent studies show that the breathing phase affects memory in humans independently of olfactory stimulation[34,257,258]. Retrieval accuracy was higher during inspiration than expiration[34], although it declined if the retrieval process spanned the expiratory-to-inspiratory phase transition[257,258]. Moreover, nasal breathing led to overall better memory performance than oral breathing[34]. Interestingly, similar improvements were observed in a study on the acquisition of odour memories: participants who breathed solely through the nose during a 1-h resting consolidation period exhibited better recognition memory than those who breathed through the mouth[259]. While the mechanisms remain unclear, this effect could reflect the influence of nasal breathing on brain oscillations — although the increased attentional demands of mouth breathing may also contribute to poorer performance.

As in rodents, the breathing phase during offline states influences the occurrence of electrophysiological patterns linked to memory consolidation in humans, such as slow oscillations and neocortical spindles[100–102]. Moreover, the strength of breathing modulation of these patterns correlates with memory reactivation[101]. Therefore, breathing may coordinate the information transfer required for memory processes during sleep in both human[100–102] and non-human[5] animals.

Perception and action

In humans, the breathing phase produces subtle yet significant modulations of perceptual and motor processes. One study demonstrated that participants spontaneously initiated a visuo-spatial perception task at the onset of inhalation, and that task performance accuracy

was significantly better during inhalation compared with exhalation[78]. Parallel EEG recordings showed that nasal inhalation altered functional network connectivity at rest and also enhanced task-related brain activity in specific regions[78]. These findings suggest that the rhythmic act of breathing primes the brain to acquire and process sensory information.

Another human experiment measured visual perception in a near-threshold detection task[260] and revealed that perception thresholds decreased during inhalation. The breathing phase-dependent changes in visual perception were closely linked to decreases in posterior alpha power (assessed by magnetoencephalography), an oscillatory activity associated with cortical excitability, where lower alpha power indicates heightened responsiveness[77]. This coupling of respiration with neural excitability may underlie the dynamic relationship between the breathing cycle and sensory processing. Relatedly, a subsequent study on tactile perception found that participants naturally adjusted their breathing cycle so that expected stimuli occurred most frequently during late inspiration and/or early expiration[261]. In turn, stimulus detection rates increased with its phase-locking to breathing[261], again suggesting that the respiratory phase optimizes sensory processing. More generally, by bridging exteroceptive and interoceptive signals, breathing has been proposed to contribute to the neural mechanisms underlying bodily self-consciousness — the experience of the body as one's own and its position in space[262,263].

Breathing is also linked to the modulation of voluntary action. Recent studies in humans indicate that the timing of voluntary movement initiation is influenced by the phase of breathing[264,265], an effect absent during externally triggered movements[264]. This breathing modulation extends beyond actual motor executions to include mental actions such as motor and visual imagery[265], suggesting a role in action preparation. Supporting this, the cortical readiness potential — a neural activity in the supplementary motor area that precedes self-initiated movements[266,267] — is also modulated by the breathing phase, during both physical[264] and mental actions[265]. Interestingly, this readiness potential begins before individuals are consciously aware of their intention to act, raising questions about the nature of voluntary movement[268].

A recent human study explored the relationship between respiration and reaction times in six sensory-cognitive tasks[269]. As expected,

Glossary

Active sensing
A process in which an organism actively controls the acquisition of sensory inputs by spending energy probing its environment (for example, sniffing, whisking, eye movements, electroreception or echolocation).

Breathing cycles
Inhalation–exhalation sequences, representing the fundamental unit of rhythmic breathing.

Central pattern generator
(CPG). A network of neurons that autonomously generates rhythmic outputs when activated, typically motor patterns such as breathing, walking or chewing.

Communication subspaces
Subsets of neurons within a brain region whose combined spiking activity is maximally correlated with that of a neuron group in another region, believed to facilitate inter-area communication.

Comodulogram
A two-dimensional colour-map representation of phase–amplitude coupling, indicating whether the amplitude of high-frequency oscillations (*y* axis) varies with the phase of lower-frequency oscillations (*x* axis).

Electroencephalography
(EEG). A non-invasive technique that records brain electrical activity via scalp electrodes, commonly used to study neural oscillations and cognitive processes in humans.

Exteroception
The sensing of external stimuli through systems such as vision, touch, hearing, taste and olfaction, providing information about the environment.

Functional MRI
A neuroimaging method that measures changes in blood flow through the blood oxygen level-dependent signal to infer brain activity across different regions.

Interoception
The sensing of internal bodily signals, such as arterial pressure, blood composition, respiratory load and visceral pain, contributing to physiological regulation, adaptive behaviour and emotion.

Intracranial recordings
Direct measurements of brain activity using electrodes implanted inside the skull, typically for high-resolution electrophysiological analysis in clinical and research settings.

Magnetoencephalography
A neuroimaging technique that detects magnetic fields generated by neuronal activity, offering high temporal resolution for studying brain function.

Neuronal oscillations
Rhythmic patterns of neuronal activity, typically measured as voltage changes in the brain, which may occur in specific frequency bands linked to various cognitive processes; also known as brain waves.

Phase–amplitude coupling
A neural interaction in which the phase of a low-frequency brain oscillation modulates the amplitude of a higher-frequency oscillation, thought to support hierarchical information processing.

Phase-locking
A phenomenon in which the phase of one oscillatory signal maintains a consistent relationship with the phase of another oscillation over time, indicating synchrony.

Spike–phase coupling
A relationship between the timing of neuronal spikes and the phase of an ongoing oscillation, reflecting coordinated activity.

Subthreshold membrane potential
The electrical potential difference across a neuron's membrane when it is below the threshold needed to generate an action potential, reflecting ongoing synaptic inputs and intrinsic cellular properties.

Working memory
A cognitive system responsible for temporarily holding and manipulating information, essential for reasoning, decision-making and goal-directed behaviour.

Box 4 | Reciprocal influences between brain states and breathing

Recent research points to a reciprocal relationship between brain states and respiratory patterns. This bidirectional communication forms a dynamic loop (see the figure; traces are schematic representations of typical recordings) in which bottom-up, reafferent breathing signals modulate brain function, whereas top-down neural signals — shaped by factors such as attention, emotion and cognitive states — adjust breathing to meet environmental and neural processing demands. This allows different brain states to fine-tune respiratory rhythms to serve adaptive purposes, such as regulating emotional responses and attentional levels, or optimizing sensory sampling, motor coordination and, potentially, memory consolidation.

Top-down control of breathing

The neocortex controls breathing through different descending pathways. In humans, the capacity for volitional breathing suggests the presence of direct descending pathways from the neocortex to diaphragm motor neurons[280]. Indeed, early work identified a region of the human motor cortex that represents the diaphragm[281–283]. More recent neuroimaging studies have shown that volitional breathing activates a network of brain regions, including the primary motor cortex, premotor cortex and supplementary motor area[105,283–285]. Electrical stimulation of some of these areas elicits short-latency responses in the phrenic nerve and diaphragm[104,282,286–289]. Thus, volitional control of breathing may bypass brainstem central pattern generators and directly stimulate diaphragmatic motor neurons[270,280,290]. Interestingly, a human study has shown that volitionally increasing the nasal breathing rate increases coherence between the breathing cycles and the breathing-coupled local field potential (LFP) rhythm in frontotemporal and insular cortices and the amygdala (AMY)[35]. Focused breathing, as in meditative practices, also increases LFP–breathing coherence, particularly in the insula and anterior cingulate cortex[35].

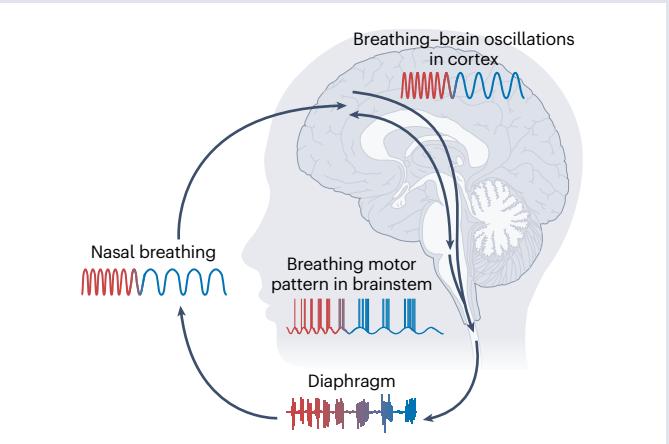
Other cortical areas modulate spontaneous breathing through indirect pathways. Initial research in rodents found that electrical and pharmacological stimulation of the medial prefrontal cortex changes respiratory patterns, with effects varying depending on the subregion[291,292]. More recently, a top-down pathway from the dorsal anterior cingulate cortex to the caudal pontine reticular nucleus that slows breathing was identified[293]. This circuit recruits inhibitory neurons in the pontine reticular nucleus that project to brainstem breathing centres. The dorsal anterior cingulate cortex→pontine reticular nucleus pathway is active during behaviours such as drinking, swimming or vocalizing, where coordinated slow breathing is essential, and is inhibited during sniffing[293]. Its activity decreases under anxiogenic conditions, whereas its optogenetic stimulation slows breathing and reduces anxiety-like behaviours[293]. These findings suggest a shared mechanism controlling breathing, behaviour and affect.

A recent study[294] reported a population of neurons expressing μ-opioid receptors in the lateral parabrachial nucleus (PBN) of mice that coordinates breathing with affective pain perception and negative emotional responses. These neurons integrate various limbic and sensory inputs, and their firing rate is positively correlated with the breathing rate. Activation of these neurons led to increased breathing rates, and heightened affective pain perception and anxiety-like behaviours, whereas inhibition produced the opposite effects. Thus, these neurons regulate breathing patterns in response to pain and also directly influence the emotional perception of pain. The neurons form two anatomically separated subpopulations in the lateral PBN that differentially project to the central AMY and the pre-Bötzinger complex (preBötC) and form a recurrent excitatory network, which probably integrates the control of affective and respiratory states.

Breathing switches brain states

Although much research has focused on how brain states influence breathing[247,295,296], ancient traditions have long recognized that breathing patterns can alter brain states. Yoga and pranayama practices[297,298], Lamaze breathing during labour[299] and mindfulness meditation[300,301] exemplify how controlled breathing can promote relaxation, alleviate pain and enhance attention. Human experience suggests that slow breathing induces feelings of calm, stress relief and increased mental clarity, and scientific research increasingly supports these claims[249,298,302–304]. Conversely, faster breathing is linked to greater arousal, anxiety and even panic attacks[305,306]. Although breathing might influence brain states through its oscillatory modulation of network activity, direct evidence for this mechanism is lacking. The respiratory rate may also indirectly influence brain states through slower autonomic and metabolic changes[251].

A recent study demonstrated that a subset of neurons in the preBötC influences the balance between arousal and calm behaviours in mice[118]. The ablation of this small neuronal group decreased breathing rates, slowed cortical activity, increased calm behaviours and reduced time spent in aroused or exploratory states. Activation of these neurons promoted arousal through excitatory projections to locus coeruleus neurons. Thus, this respiratory neuronal subgroup promotes arousal when breathing rates increase, while allowing for relaxation during slow and regular breathing.



participants naturally aligned their breathing cycle with the task demands, tending to inhale around stimulus presentation and exhale when responding, with reaction times consistently varying across the respiratory cycle[269]. Overall, certain phases of the breathing cycle seem to create windows in which the neocortex is better prepared to perceive, plan or act. Moreover, the growing body of evidence indicates that breathing modulates not only sensory perception and motor activity but also higher-level cognitive processes.

Conclusions and future directions

Over the past decade, the perennial and vital rhythm of breathing has emerged as a global modulator of brain activity across mammals. In this Review, we have summarized the current evidence showing how breathing orchestrates neuronal dynamics over multiple organizational levels, extending its effects beyond olfactory and respiratory centres, and have discussed the underlying mechanisms and potential functional roles. We have shown how nasal airflow is necessary and sufficient to drive global breathing–brain signals through cyclically activating olfactory sensory neurons. This sequence of evoked potentials propagates through the brain, giving rise to a neuronal oscillation that is independent of classical endogenous brain rhythms, such as delta and theta. Whether sources other than nasal airflow, such as corollary discharges or interoceptive signals, contribute to respiratory modulation of the brain above the thalamus is still unclear, as experiments selectively manipulating these alternative candidate pathways are still missing.

What are the functional roles of these evolutionarily conserved respiratory brain rhythms? We have discussed how some could be similar to the proposed roles of other neuronal oscillations — organizing neuronal activity in time and promoting communication between areas — and reviewed evidence that these mechanisms could be contributing to emotional responses and memory. Other functions could be specifically related to the origins of breathing–brain signals; rhythms of nasal origin will carry information on breathing and olfaction and can contribute to sensory coding and binding. Dissecting the roles of respiratory brain rhythmicity from the specific information carried from its sources will be especially challenging. In humans, perception and action are subtly affected by the phase of the nasal breathing cycle, hinting that our brain circuits are, to some degree, paced by the breathing rhythm. Breathing has long been known to influence emotion and cognition, but, overall, we are still a long way from understanding whether and how breathing–brain signals contribute to these phenomena.

Whereas fundamental aspects of breathing–brain interactions appear to be conserved across mammals, differences in breathing patterns, voluntary control and olfactory reliance probably lead to species-specific effects. In rodents, a stronger olfactory drive may exert a greater influence on brain activity, whereas in humans, slower breathing rates enable amplitude modulations of lower-frequency oscillations than in rodents, such as delta and alpha. Extending comparative studies to non-mammalian species could provide further valuable insights by contrasting the extent of breathing–brain interactions with different ethological demands.

A promising research avenue lies in further characterizing the bidirectional nature of breathing–brain interactions. Although the reafferent breathing rhythm exerts bottom-up influences on neuronal and circuit dynamics, recent research also points to a top-down modulation of respiratory patterns by brain states (Box 4). Better understanding the nature of this loop may help in exploring its translational potential. How might the modulation of breathing rhythms improve therapies for anxiety, depression and cognitive impairments? Similarly, could breathing–brain signals be harnessed to enhance learning, memory or motor performance?

We have taken big steps in unveiling the modulation of neural activity by breathing. Looking into the future, outstanding questions remain regarding the role of breathing-coupled oscillations in the complex interplay between our brains and the rest of our bodies.

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