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"Brain–breath" interactions: respiration-timing–dependent impact on functional brain networks and beyond

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Abstract: Breathing is a natural daily action that one cannot do without, and it sensitively and intensely changes under various situations. What if this essential act of breathing can impact our overall well-being? Recent studies have demonstrated that breathing oscillations couple with higher brain functions, i.e., perception, motor actions, and cognition. Moreover, the timing of breathing, a phase transition from exhalation to inhalation, modulates specific cortical activity and accuracy in cognitive tasks. To determine possible respiratory roles in attentional and memory processes and functional neural networks, we discussed how breathing interacts with the brain that are measured by electrophysiology and functional neuroimaging: (i) respiration-dependent modulation of mental health and cognition; (ii) respiratory rhythm generation and respiratory pontomedullary networks in the brainstem; (iii) respiration-dependent effects on specific brainstem regions and functional neural networks (e.g., glutamatergic Pre-Bötzinger complex neurons, GABAergic parafacial neurons, adrenergic C1 neurons, parabrachial nucleus, locus coeruleus, temporoparietal junction, default-mode network, ventral attention network, and cingulo-opercular salience network); and (iv) a potential application of breathing manipulation in mental health care. These outlines and considerations of "brain–breath" interactions lead to a better understanding of the interoceptive and cognitive mechanisms that underlie brain–body interactions in health conditions and in stress-related and neuropsychiatric disorders.

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1 Introduction

We have control over our own bodies and can perform actions voluntarily as planned and expected. For example, as reading this sentence, we are moving our eyes across the text and wondering about what we are about to read next. Such regulatory mechanisms of brain function are defined in a "top-down" fashion. Alternatively, we hear our own heartbeats racing when we stand in front of a large audience when playing baseball or making a symposium presentation. Such heartbeats are involuntarily regulated according to autonomic mechanisms based on the roles of homeostasis and allostasis and are defined as vegetative functions in a "bottom-up" fashion. Pertinently, there are interoceptive pathways that influence brain function (Critchley and Harrison 2013). Regarding the concept of the brain as a prediction machine (i.e., the free-energy principle; Friston 2009; Seth 2013), it has been hypothesized that when afferent interoceptive inputs are noisy or imprecise, top-down predictions reduce attention to mismatch or ignore bottom-up inputs, which convey prediction errors (Barrett and Simmons 2015). This misinterpretation may cause prolonged or inadequate responses of molecular and physiological mechanisms, resulting in allostatic load, cognitive deficits, and stress disorders (McEwen 1998; McEwen and Akil 2020). It remains unclear whether top-down regulation can precisely coordinate bottom-up regulation.

Breathing is a natural process that we cannot live without; however, it is also said that breathing is a daily action that sensitively and intensely changes under various situations. The respiratory control system is unique and distinct from other autonomic systems because it operates through innervation with top-down voluntary regulation via the anterior cingulate cortex (ACC, Devinsky et al. 1995; Hassan et al. 2013). Recent studies have provided evidence on how the electrophysiological activity of the brain, perception, motor actions, and cognition depend on the phase of the respiratory cycle (Figure 1, Boyadzhieva and Kayhan 2021; Jerath and Beveridge 2020; Maric et al. 2020; Parviainen et al. 2022).

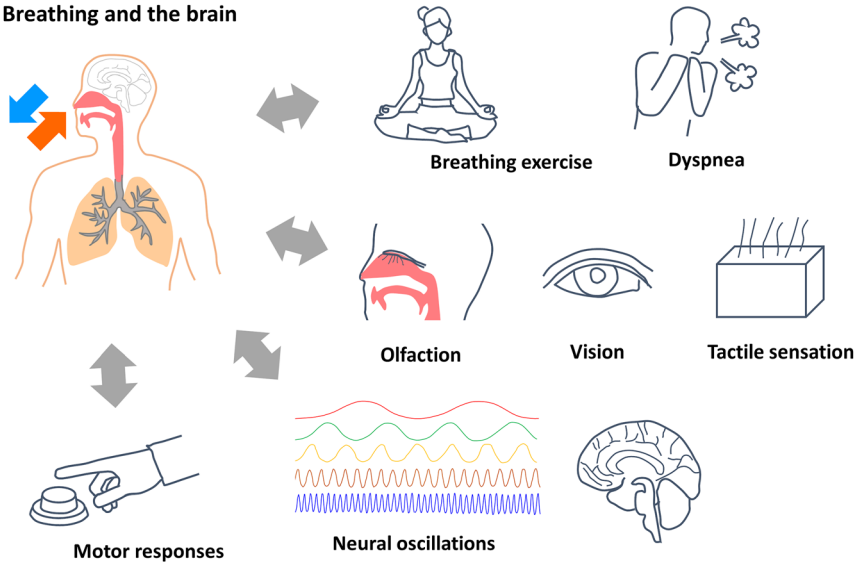

Figure 1: A crosstalk interaction between breathing and brain function. Breathing and the brain have crosstalk interactions. Brain states are changed by breathing exercises and dyspnea. Respiration couples with olfaction, vision, tactile sensation, and cortical neural oscillations. Furthermore, successful motor responses in cognitive tasks are associated with certain times during the respiratory cycle.

Slow breathing techniques promote autonomic and psychophysiological changes in brain–body interactions to reduce symptoms of arousal, anxiety, and depression (Zaccaro et al. 2018). Noble and Hochman (2019) hypothesized that pulmonary afferent activity during breathing at a low frequency (i.e., 0.1 Hz) contributes to modulation of physiological processes and supports brain oscillations to induce the default-mode network (DMN, Menon 2011; Menon and Uddin 2010; Raichle et al. 2001). Oku (2022) described that the breathing process has complex variability that is caused by the respiratory central pattern generator (CPG) and higher brain centers and discussed hidden information that can be translated in clinical practice for diagnosis, emotion, and mental conditioning. We recently found that breathing changes the accuracy of cognitive tasks; i.e., the accuracy of a delayed matching-to-sample (DMTS) task was decreased when the retrieval process spanned the onset of inhalation, equivalent to the exhalation-to-inhalation (EI) transition, during the respiratory cycle (Nakamura et al. 2022, 2018). Notably, we showed that, during the retrieval process, the inspiratory onset- or EI transition–dependent effects were relevant to activation in specific cortical regions, specifically the temporoparietal junction (TPJ, also known as the supramarginal gyrus and inferior parietal lobule or IPL; Nakamura et al. 2022), which is a neural core of the ventral attention network (VAN) and has preferential functional connectivity to the cingulo-opercular network (CON; Corbetta et al. 2008; Igelström and Graziano 2017). Related to these findings, we reviewed several interacting issues between breathing and brain function. First, we introduce phenomena in which breathing affects mental health and couples with attention, perception, motor actions, and cognition. Second, we explain neural mechanisms generating respiratory activity and phase components in the brainstem and respiratory pontomedullary networks. Third, we introduce the primary human neuroimaging method of functional magnetic resonance imaging (fMRI), which can cause respiratory artifacts in blood oxygen level–dependent (BOLD) signals, and then describe how to interpret BOLD signals without respiratory artifacts. Finally, we discuss the potential roles of respiration that spontaneously changes large-scale brain network activity and how it could be applied as a possible mental health treatment to reduce or eliminate symptoms of stress-related and neuropsychiatric disorders.

2 Respiration and brain states

2.1 Lower frequency breathing

Historically, the act of breathing has been long believed to shape the mind and affect mental conditions. Breathing exercises, such as slow-deep breathing and focusing each breath, modify cardiovascular and brain functions and consequently improve mental health and cognitive and motor performance (Bing-Canar et al. 2016; Dick et al. 2014; Fincham et al. 2023; Yadav and Mutha 2016). Breathing exercises are typically incorporated in training methods for Zen meditation and yoga, such as transcendental meditation, 4-7-8 breathing, and Sudarshan kriya yoga, and are used to alleviate psychiatric and other stress-related medical conditions (e.g., Brown et al. 2013; Brown and Gerbarg 2009). Noble and Hochman (2019) propose that breathing at a frequency near 0.1 Hz may promote behavioral relaxation and baroreflex resonance effects. Slow-deep inhalation activates slowly adapting pulmonary stretch receptors (SARs), which

end inspiration and facilitate expiration as part of the Breuer–Hering reflex (Kubin et al. 2006). SARs have been implicated in the regulation of airway smooth muscle tone, the regulation of systemic vascular tone and heart rate, and the pathophysiology of restrictive lung disease (Schelegle 2003). This model for breathing-dependent relaxation assumes a physiological process of SAR pathways through the nucleus tractus solitarious (NTS) with connectivity to central autonomic networks. Although fMRI data processing methods may not completely separate respiration-related signals from DMN activity and this component may be reflected to some degree, the DMN with a low frequency (<0.1 Hz) was highly correlated with respiration-related signals (Birn et al. 2008a). Thus, voluntary deep breathing may modulate the autonomic nervous system via SAR activity in the lungs, resulting in eliciting resonant and coherent features in neuromechanical interactions that optimize physiological and brain states (Noble and Hochman 2019).

2.2 Respiratory sinus arrhythmia (RSA)

The other well-known phenomenon of the periodic activity of respiration on physiological function is respiratory sinus arrhythmia (RSA), which is a variation in the R-wave to R-wave (RR) interval between heartbeats in accordance with inhalation and exhalation (Eckberg 2003; Larsen et al. 2010). In the respiratory cycle, the RR interval shortens during inhalation and lengthens during exhalation at a resting state in humans (Gilad et al. 2005; Tzeng et al. 2009) and in free moving animals (Bouairi et al. 2004). The power spectrum of this phenomenon is also known as heart rate variability (HRV), which is tightly linked to the frequency of RSA. HRV biofeedback is applied as a treatment for a variety of disorders and for performance enhancement (Lehrer and Gevirtz 2014). HRV is influenced by breathing frequency, and maximum effects are usually achieved when breathing at a rate of approximately 0.1 Hz. Meanwhile, mental stress induced incoherent oscillations with respect to breathing, in addition to an attenuation of RSA (Niizeki and Saitoh 2012). Thus, methodologically, phase synchronization between respiration and RSA (i.e., individual values of RSA amplitude) could provide an appropriate measure for evaluating physiological and mental stress states. Indeed, Denver et al. (2007) showed that the amplitude of RSA is modulated by the muscarinic acetylcholine receptor antagonist atropine, but the frequency of RSA is not. However, the difference in methodological approaches for RSA is yet to be elucidated.

A mechanism generating RSA has been identified in the pontomedullary networks (Dergacheva et al. 2010). At least three sites, the medullary NTS, nucleus ambiguus, and pontine Kölliker-Fuse nucleus (KFN), arise independently of RSA (Farmer et al. 2016). The principal preganglionic vagal motoneurons, which are mainly distributed in the nucleus ambiguus, receive glutamatergic and GABAergic afferent projections and regulate heart rate. The firing pattern of cardiac vagal motoneurons is known to be tonically active, with a synchronous pattern of the cardiac pulse (Dergacheva et al. 2010). Importantly, the pattern of the cardiac pulse fluctuated by GABAergic afferent inputs, due to cholinergic innervation at their presynaptic terminals. During inhalation, the presynaptic terminals of GABAergic synaptic inputs, which have projections to cardiac vagal motoneurons, are facilitated by cholinergic activation via beta 2 nicotinic receptors (Neff et al. 2003; Wang et al. 2003), resulting in a shortened RR interval. During exhalation, the RR interval was extended due to the suppression of these cholinergic inputs. Accordingly, RSA is a critical factor of the cardiovascular system induced by respiratory oscillations.

2.3 Attention to breathing and dyspnea

There is substantial evidence that breathing contributes to improvements in brain states. Human neuroimaging studies showed that spontaneous breathing was coordinated with periodic brain activity during resting states, which were measured by fMRI (Yoshikawa et al. 2020) and magnetoencephalography (MEG; Kluger and Gross 2021a). Other studies using intracranial electroencephalography (iEEG) and fMRI indicated that when healthy volunteers paid attention to their breathing, respiration–brain signal coupling (i.e., respiration-iEEG coherence and respiration-fMRI signal synchronization) was increased in the insula, ACC, premotor cortex, and hippocampus (Herrero et al. 2018; Wang et al. 2019). Respiration-iEEG coherence was also increased in the frontotemporal-insular network when healthy participants breathed at a voluntary and slightly faster rate (Herrero et al. 2018). Respiratory sensation is likely to involve the insula, which is known as a central hub for interoception (Chen et al. 2021; Craig 2003; Evrard 2019).

Dyspnea is a feeling of chest tightness and difficulty breathing on inhalation, and it is distinguished from the breathlessness we would observe in normal subjects, such as that induced by exercise. Dyspnea is defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity (American Thoracic Society 1999; Fukushi et al. 2021; Parshall et al. 2012). Notably, a human lesion study demonstrated that the insula was associated with sensitivity to dyspnea and pain: patients

with lesions of the right insula showed reduced sensitivity in the perception of unpleasant sensations, particularly in the perception of dyspnea and pain (Schön et al. 2008). Dyspnea and palpitations can be compulsorily caused by infusion of isoproterenol, an agonist of peripheral beta-adrenergic receptors. Hassanpour et al. (2018) found that the injection of isoproterenol led healthy volunteers to exhibit increased dyspnea and palpitations with concomitant fMRI activation of the right insula. During the recovery process, fMRI activation of the right insula spread from the right anterior insula to the right posterior insula and to the left middle insula. Von Leupoldt et al. (2008) revealed that the respiratory load can induce activation of the insula. Negative emotional stimulation (i.e., viewing a standardized emotional picture series from the International Affective Picture System or IAPS Database, Lang et al. 2005) successfully induced respiratory load, which was associated with higher levels of unpleasantness of perceived dyspnea when compared with respiratory load during positive emotional stimulation. Then, a negative emotional–stimulated respiratory load increased fMRI activation in the right anterior insula and right amygdala, suggesting that dyspnea-related unpleasantness is processed in the right anterior insula and amygdala (von Leupoldt et al. 2008). Accordingly, these findings indicate that the right anterior insula and its associated regions may play a crucial role in respiratory sensation and dyspnea.

In terms of medical psychiatric phenomena, chronic obstructive pulmonary disease (COPD) is a respiratory disease that chronically causes airflow blockage and breathing-related problems and is associated with a high incidence of anxiety and panic attack symptoms (Mikkelsen et al. 2004; Pumar et al. 2014). The breathing pattern is exaggerated in excess of metabolic need and can cause dyspnea and, as a result, bring on panic attacks in patients (Freire et al. 2010). These patients can misinterpret normal bodily sensations and become almost obsessively focused on something being wrong (Mikkelsen et al. 2004). It is suggested that this misinterpretation might be associated with dysfunction or overactivity of the anterior insula that is implicated in anxiety disorders characterized by burdensome preoccupation with somatic symptoms (Wolters et al. 2022).

2.4 Respiration and perception

It is said that breathing contributes to the detection of sensory information from the outside world. Rodent studies have shown that sniffing or sampling of olfactory information is coordinated during the respiratory cycle (Uchida and Mainen 2003). In awake rats, activity of the mitral and tufted cells in the olfactory bulb was coupled to certain times of inhalation, resulting in successful odor discrimination (Cury and Uchida 2010; Shusterman et al. 2011). Whisking (vibrissa touch) detection was phase-locked to certain times of exhalation, in coordination with a phase shift of sniffing to compensate for output from the olfactory bulb (Curtis and Kleinfeld 2009; Kleinfeld et al. 2014). Human studies have identified a similar tendency in respiratory phase locking to sensation, i.e., olfaction, touch, and vision. Odor detection occurring during inhalation was phase-locked to alpha oscillations, but it was not seen in the inspiration-triggered potentials of normal breathing (Masaoka et al. 2005). Respiratory phase locking to tactile sensation showed the highest detection rate during the early phase of exhalation (Grund et al. 2022). Visual signals presented during exhalation were detected more frequently than those presented during inhalation (Flexman et al. 1974). A recent study using MEG found that the sampling of visual information was preferentially aligned with cortical activity at a certain point in the respiratory phases to facilitate visual sensitivity (Kluger et al. 2021b). Notably, maximized cortical activity occurred during the late phase of inhalation. Although respiratory phase locking to sensory detection was occasionally shifted at certain times during the respiratory cycle, respiration may play an important role in enhancing discrimination rates of sensory information.

2.5 Respiration and neural oscillations

Numerous studies using laboratory rodents have determined cross-frequency coupling between breathing and brain oscillatory activity (Heck et al. 2019; Tort et al. 2018), the latter of which was measured by local field potential (LFP) and electroencephalography (EEG, Buzsaki et al. 2012). In rodents, the respiratory rhythm entrains neural oscillatory ranges for delta (0.5–4 Hz), theta (4–12 Hz), and gamma (30–80 Hz) in the olfactory bulb and extensive cortical regions, i.e., the piriform cortex (Fontanini et al. 2003), barrel cortex (Ito et al. 2014), hippocampus (Chi et al. 2016; Liu et al. 2017; Lockmann et al. 2016; Yanovsky et al. 2014), prefrontal cortex (Biskamp et al. 2017; Zhong et al. 2017), and posterior parietal cortex (Jung et al. 2022). Respiration-coupled oscillations in the brain (i.e., phase-phase coupling), which were identified in mice in awake states, were slow in their synchronized frequency (i.e., delta oscillations) during immobility and were faster (i.e., theta oscillations) during exploratory behavior (Biskamp et al. 2017; Zhong et al. 2017). Respiration-delta/theta coupling in rodents was abolished by breathing after olfactory bulbectomy (Biskamp et al. 2017; Ito et al. 2014) or with direct trachea airflow instead of nasal

airflow (tracheotomy, Lockmann et al. 2016; Yanovsky et al. 2014), suggesting that the airflow in the respiratory system through the nasal cavity may be essential for the formation of respiration-delta/theta coupling. Although the respiratory frequency is determined by the body size of mammals during awake states (i.e., 3–7 Hz in mice, 1–3 Hz in rats, and 0.15–0.3 Hz in humans), respiration-locked activity occurs in the human brain, i.e., the piriform cortex and hippocampus in epilepsy patients, as determined using iEEG recordings (Herrero et al. 2018; Zelano et al. 2016). In an extensive analysis of human data, the phase–phase coupling between respiration (i.e., 0.15–0.3 Hz) and hippocampal LFP was detected at 0.28 Hz (Tort et al. 2018). Moreover, while respiration coupled with gamma oscillations in the hippocampus and prefrontal cortex (i.e., phase-amplitude coupling, Biskamp et al. 2017; Ito et al. 2014; Yanovsky et al. 2014; Zhong et al. 2017), theta-gamma coupling in the hippocampus and prefrontal cortex is associated with successful cognitive performance in rodents (Schomburg et al. 2014; Tamura et al. 2017; Tort et al. 2009) and humans (Axmacher et al. 2010; Friese et al. 2013; Köster et al. 2014). Importantly, the disappearance of respiration-delta/theta coupling diminished gamma oscillations in mice (Ito et al. 2014). Hence, respiration-delta/theta coupling might be crucial for the generation of gamma oscillations during cognitive brain states (Tort et al. 2018).

2.6 Respiration and motor actions

Studies of animal ecology have revealed that respiration is phase-locked to locomotion in wild mammals. For instance, a wallaby runs across the prairie field while hopping with both feet together. The ratio of breathing to hopping is phase-locked at a 1:1 ratio, whereas the heart rate is not synchronized with hopping (Baudinette et al. 1987). In bats, the ratio of breathing to wing flapping is synchronized at a 1:1 ratio (Carpenter 1986). A dog coordinates diaphragmatic oscillations and chest wall deformation during trotting behavior (Bramble and Jenkins Jr 1993). In humans, numerous studies have shown that the respiratory phase reflects walking, running, and successful motor actions. When healthy volunteers started manipulating an object with their fingers, performance accuracy was dependent on coordination in either inhalation or exhalation with internal representations during either adaptative or predictive processes (Lamberg et al. 2003; Mateika and Gordon 2000). Notably, Park et al. (2020) demonstrated that voluntary motor actions were preferentially initiated during the late phase of exhalation, and one-at-a-time cortical activity was coordinated with motor actions. In healthy volunteers performing memory tasks and discrimination tasks, button-press responses by fingers occurred more frequently during exhalation (Johannknecht and Kayser 2022) and the late phase of exhalation (Nakamura et al. 2022). However, simple, externally triggered actions did not show respiratory phase locking (Park et al. 2020). Thus, successful motor responses in cognitive tasks are likely associated with certain times during exhalation.

2.7 Respiration and cognitive processes

Considerable evidence has been provided on how respiration modulates cognitive processes and cognitive brain function. Cognitive processes are a mixture of subprocesses during online brain states, e.g., attention, encoding, retrieval, and decision-making, as well as offline brain states, e.g., sleep and consolidation. Human studies have shown that nasal respiration during encoding, consolidation, and retrieval of recognition memory tasks increased accuracy compared to oral respiration (Arshamian et al. 2018; Zelano et al. 2016). However, phase-dependent effects of respiration (e.g., inhalation vs. exhalation) on accuracy are more complicated (Johannknecht and Kayser 2022; Zelano et al. 2016). In an eyeblink conditioning task in healthy volunteers, the rate of conditioned responses was higher when they were trained at exhalation compared to inhalation (Waselius et al. 2019). Zelano et al. (2016) found that accuracy was higher when test cues (i.e., retrieval cues) were presented during inhalation than exhalation in a recognition memory task. Notably, retrieval and recognition processes have an array of cognitive subprocess components, e.g., accessing what-where-when information, components of accessibility and availability, and match and mismatch processes (Clayton et al. 2003; Eichenbaum et al. 2007; Gardiner 2007). Thus, a key component must be whether the retrieval process crosses phase transitions during the respiratory cycle, i.e., the EI transition (onset of inhalation or inspiratory onset) and inhalation-to-exhalation (IE) transition (onset of exhalation or post-inspiratory onset), at which different sets of respiratory neurons in the brainstem start firing synchronously (Richter and Smith 2014; Smith et al. 2013). Indeed, Perl et al. (2019) showed that accuracy was increased when test cues were presented at the exact time of EI transition (inspiratory onset) than at the exact time of IE transition (postinspiratory onset) in a visuospatial task (or mental-rotation task).

We have provided evidence that phase transitions (i.e., EI transition vs. IE transition) differentially affect accuracy and reaction time (RT) when the retrieval process spans each transition during the DMTS recognition memory task with a short delay (Nakamura et al. 2022, 2018). RT is

a popular measure of cognitive function and refers to the duration between the presentation of a sensory cue (e.g., light or sound) and a button-press response in cognitive tasks. RT is a critical indicator of discrimination ability and reflects task difficulty. Our findings showed that accuracy was reduced and RT was extended when the retrieval process spanned the EI transition (inspiratory onset) compared to other respiratory components (e.g., post-inspiratory onset), suggesting that the EI transition must be a key component for modulating cognitive performance and brain function. We propose that the EI transition might play critical roles as both a "reset and trigger" during cognitive processes, possibly leading to increased accuracy when the EI transition starts at the onset of the process (Perl et al. 2019) and decreased accuracy when the EI transition occurs in the middle of the process (Nakamura et al. 2018, 2022). Next, we discuss the neural mechanisms generating the EI and IE transitions during respiratory cycles.

3 Neural mechanisms of respiratory rhythm generation

3.1 Respiratory central pattern generator (CPG)

It has been suggested that respiratory CPGs determine breathing activity, which alternates between inhalation and exhalation with combinations of tidal pressure (amplitude) and phase duration (time), although the complete picture of the respiratory CPG remains unclear (Okada et al. 2020). Experiments for the living brain have limitations since the adult brain is extremely sensitive to the state of oxygenation. Thus, neonatal brain slice preparation is commonly used for determination of the respiratory rhythm generator. Using neonatal slices of the brainstem, the primary inspiratory rhythm generator was found in the PreBötzinger complex (PreBötC), which is a bilateral neuronal nucleus in the ventrolateral medulla (Smith et al. 1991). On the other hand, the expiratory rhythm generator was identified in the parafacial respiratory group (also known as the lateral parafacial nucleus, Onimaru and Homma 2003), which is bilaterally located ventrolateral to the facial nucleus in the medulla and partially overlaps with the retrotrapezoid nucleus. However, since the parafacial respiratory group appears to be quiescent in adult intact rodents and generates late-expiratory bursts conditionally (Huckstepp et al. 2015; Janczewski and Feldman 2006), the PreBötC is considered the kernel for respiratory rhythm generation (Feldman et al. 2013; Smith et al. 2013).

3.2 A neural mechanism of the exhalation-to-inhalation (EI) transition

A neural mechanism that generates respiratory oscillations and phase transitions (i.e., EI and IE transitions) is anatomically and physiologically different (Figures 2 and 3). The respiratory cycle, meaning alternation between inhalation and exhalation, is formed by dynamic interactions between excitatory and inhibitory neurons of the respiratory CPG and the pontomedullary networks (Figure 2a, Del Negro et al. 2018; Dutschmann and Dick 2012; Richter and Smith 2014; Smith et al. 2013). The respiratory cycle consists of three distinct phases (Figure 2b): inspiration (inhalation), post-inspiration (the early phase of exhalation), and active expiration (E2, the late phase of exhalation). Hence, the EI transition and IE transition are defined by the onsets of inspiration and postinspiration, respectively. "Medullary" respiratory oscillators, causing a biphasic inspiratory–expiratory rhythm, are composed of networks between inspiratory excitatory neurons (i.e., Pre-I/I neurons, Figure 2a) in the PreBötC and the "inhibitory ring" of three types of inhibitory neurons (i.e., Early-I, Post-I, and Aug-E neurons) in the PreBötC and adjacent Bötzinger complex (Richter and Smith 2014). During inspiration, the subpopulation of inspiratory excitatory neurons (Pre-I/I neurons), which are bilaterally connected to glutaminergic neurons (Koizumi et al. 2013; Koshiya et al. 2014), persistently bursts intrinsically even when the PreBötC is isolated *in vitro* in a slice from a neonatal rodent medulla (Figure 3a and b, Koshiya and Smith 1999; Smith et al. 1991). As demonstrated, according to the property of excitatory neurons in the PreBötC, the EI transition can be generated in an "divergent manner" (see Figure 3a).

3.3 A neural mechanism of the inhalation-to-exhalation (IE) transition

A resetting of oscillatory processes provides gate control of neuronal excitability that irreversibly terminates inspiration and blocks afferent excitatory synaptic input from the network and periphery and then starts the IE transition and subsequent postinspiration (Figure 3c–e, Richter and Smith 2014). Numerous studies suggest that the postinspiration

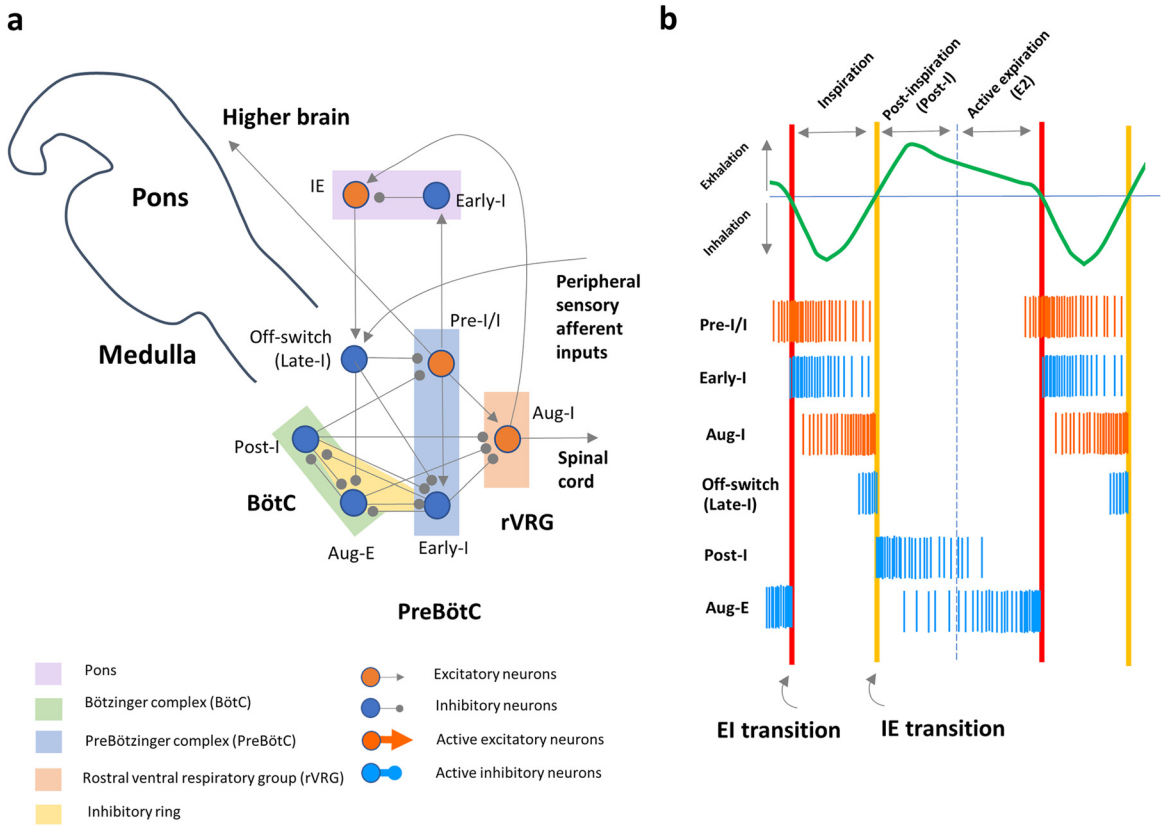

Figure 2: Spatiotemporal neural mechanisms of respiratory rhythm generation (1). (a) Schematic drawing showing network connectivity with subtypes of respiratory neurons in the medulla and pons (Dutschmann and Dick 2012; Richter and Smith 2014; Smith et al. 2013). (b) Drawing showing firing patterns of individual respiratory neurons in the medulla during the respiratory cycle (Richter and Smith 2014; Smith et al. 2013). A respiratory waveform, a green line; the exhalation-to-inhalation (EI) transition, red lines; the inhalation-to-exhalation (IE) transitions, yellow lines; excitatory neurons, bundles of orange lines; and inhibitory neurons, bundles of blue lines.

phase can be caused by an inspiratory off-switch mechanism via (i) the sensory feedback from the inflated lung arising from the pulmonary stretch receptor (e.g., SARs), known as the Breuer–Hering reflex (Kubin et al. 2006), and (ii) intrinsic synaptic mechanisms in the pons (Dutschmann and Dick 2012). In particular, the inspiratory off-switch is initiated by phasic or tonic firing neurons (i.e., IE neurons) in the KFN and adjacent subnuclei of the parabrachial nucleus (PBN) in the pons (Figure 3c, Ezure and Tanaka 2006; Richter and Smith 2014). Then, postinspiratory neurons (i.e., Post-I neurons) in the Bötzinger complex fire to prevent the lungs from abrupt deflation during the postinspiratory phase (Figure 3d).

Anderson et al. (2016) also demonstrated that excitatory neurons in the intermediate reticular nucleus in the medulla function as independent oscillators of the post-inspiratory complex (PiCo) with rhythm-generating but distinct modulatory properties. As a result, it is believed that the PiCo might independently contribute to the generation of postinspiratory behaviors, such as swallowing and vocalization (Del Negro et al. 2018; Ramirez and Baertsch 2018). However, the blockade of these excitatory activities by the $GABA_A$ receptor agonist isoguvacine did not cause prolongation of inspiration or apneusis (Toor et al. 2019). Thus, the hypothesis of the PiCo as an independent oscillator remains under debate.

On the other hand, bilateral lesions of the KFN in the pons or vagotomy (for the Breuer–Heiring reflex) cause severely prolonged inspiration or apneusis and can destroy the timing of the inspiratory off-switch (Dutschmann and Dick 2012; Smith et al. 2007). These findings indicated that either KFN input or vagal afferent input, or both, act through the inspiratory off-switch mechanism involved in the proper timing of IE transition. Nevertheless, apneusis after KFN lesions and vagotomy was not permanent because networks outside the sensory-pontine loop compensate for the lack of the function of the inspiratory off-switch and perhaps because afferent inputs from cortical regions (i.e., ACC) control conscious and behavioral adjustment of breathing (e.g., Devinsky et al. 1995; Hassan et al. 2013). As a result of an

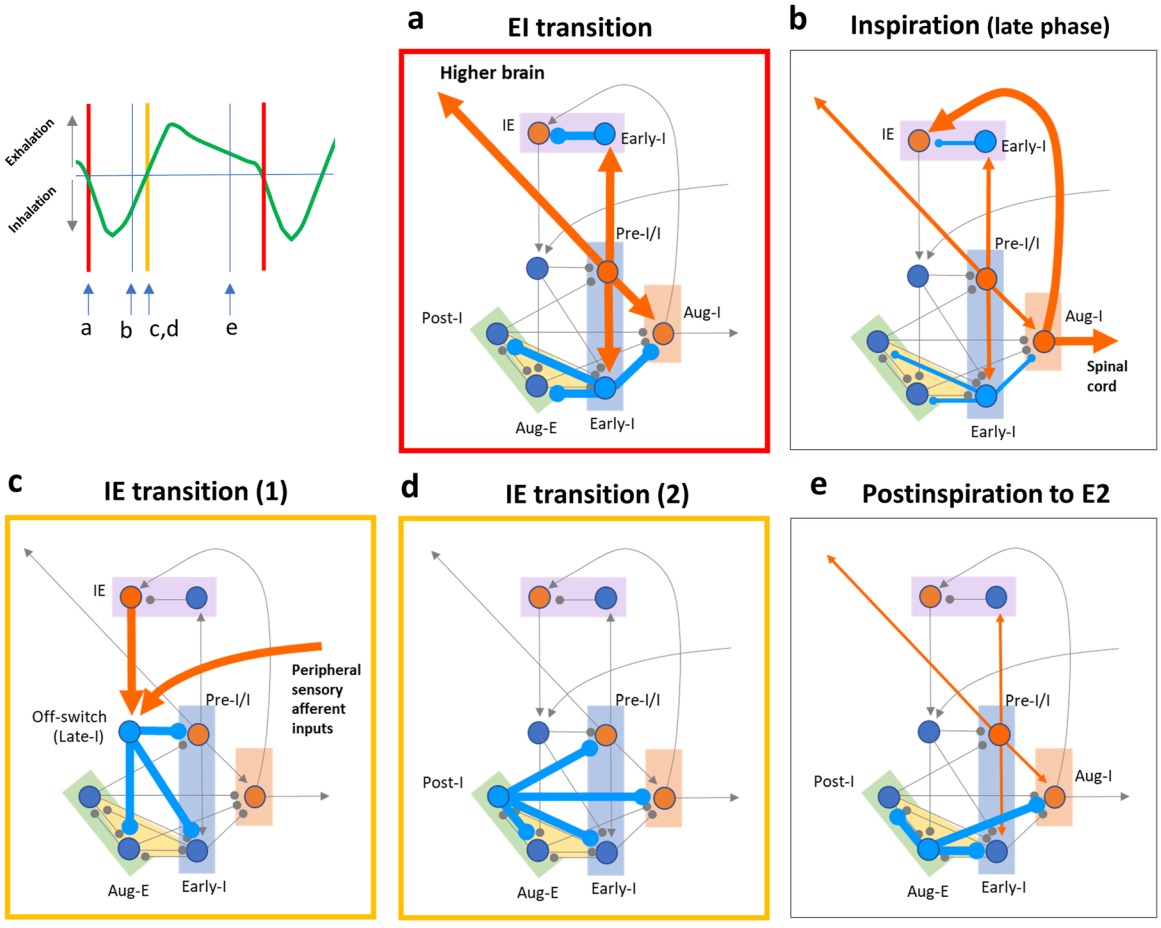

Figure 3: Spatiotemporal neural mechanisms of respiratory rhythm generation (2). Drawing showing combinations of firing patterns of respiratory neurons at each phase during the respiratory cycle (left upper panel). (a) At the EI transition (a red rectangle), excitatory Pre-I/I neurons (orange) in the PreBötzinger complex (PreBötC) activate inhibitory Early-I neurons (blue) in the PreBötC and pons. (b) Excitatory Aug-I neurons (orange) in the rostral ventral respiratory group (rVRG) fire during the late phase of inspiration. (c and d) At the IE transition (yellow rectangles), excitatory IE neurons (orange) in the pons and peripheral sensory afferent inputs activate inhibitory off-switch neurons (Late-I neurons, blue) in the medulla, and then inhibitory Post-I neurons (blue) fire in the BötC. (e) Inhibitory Aug-E neurons (blue) fire in the BötC during postinspiration and active expiration (E2).

irreversible termination setup from a diversity of neural networks within and outside the pontomedullary region, the IE transition is implied to be generated in a "convergent manner" (see Figure 3c and d).

4 Respiration and functional brain networks

4.1 BOLD signal measured by fMRI

To date, respiration-dependent effects on the human brain have been identified using functional neuroimaging approaches characterized by different temporal and spatial resolutions, such as noninvasive EEG (Masaoka et al. 2005; Perl et al. 2019), intracranial EEG (Herrero et al. 2018; Zelano et al. 2016), MEG (Kluger and Gross 2021a; Kluger et al. 2021b), positron emission tomography (PET), and fMRI. An early PET study showed that active inhalation and active exhalation induced activation in the primary motor cortex and supplementary motor area (SMA; Ramsay et al. 1993). There is a growing consensus that fMRI is the primary functional neuroimaging method in human research that can determine task-related activation and resting-state functional connectivity. BOLD contrast is known as the fMRI signal (Ogawa et al. 1990), which is a complex hemodynamic response function (HRF). Although the relationship between BOLD signals and neural activity remains a matter of debate (Iadecola and Nedergaard 2007; Logothetis et al. 2001; Kim and Ogawa 2012; Viswanathan and Freeman 2007), BOLD signals can be an indicator of synchronous neural activity.

Since fMRI signals sensitively reflect cerebral CO_2 fluctuations and breathing patterns, fMRI data targeting respiration-dependent effects must be processed carefully so that the data are appropriately interpreted as neural activity (e.g., Power et al. 2020).

4.2 Respiratory artifacts in BOLD signals

Changes in BOLD signals accurately reflect neural activity if the intermediate vascular steps are not significantly altered (Murphy et al. 2013). Arterial CO_2 concentration alters with respiratory depth and rate, leading to BOLD signal changes that are unrelated to neural activity. Such fluctuations in arterial CO_2 concentration cause variations in respiration volume per time (RVT; Birn 2012; Birn et al. 2006, 2008b). In particular, deep breathing and breath holding strongly contribute to BOLD signals, which reflect a severe respiratory artifact (Huijbers et al. 2014; Power et al. 2020). Huijbers et al. (2014) showed that retrieving visual items that were encoded during a 20-s period of breath hold decreased fMRI activation in the posterior midline brain region compared with retrieving items that were encoded during spontaneous breathing (Huijbers et al. 2014). Meanwhile, no difference in fMRI activation was observed in the ventrolateral prefrontal cortex between breath holding and spontaneous breathing conditions. Notably, the effects of deep breath, breath hold, and RVT can be mostly regressed out using the AFNI program of the RetroTS algorithm (Birn et al. 2009, 2008b, 2006; Power et al. 2020). However, phasic neural activity derived from the respiratory center of the pontomedullary networks remains problematic to interpret as BOLD-related neural activity.

A time series of BOLD-related neural activity is usually detected by a neural model convolved with canonical HRF using the general linear model (Friston et al. 1994; Worsley and Friston 1995). Since BOLD signals contain noise and anatomical and physiological artifacts that are unrelated to neural activity, fMRI data are generally processed through multiple steps of normalization and denoising, such as by independent component analysis (ICA)-based denoising of time series data using multirun application of FMRIB's ICA-based Xnoiseifier (multirun ICA-FIX; Griffanti et al. 2017; Nakamura et al. 2022; Okamoto et al. 2020). Recently, the multirun ICA-FIX approach has gained attention: a time series of fMRI data was divided into spatial map, temporal map, and power spectrum components and classified as either signal or noise components semiautomatically based on certain criteria (see Griffanti et al. 2014, 2017). In particular, the cardiac and respiratory cycles, which appear as low-frequency fluctuations at approximately 1 Hz and 0.3 Hz, respectively, can be extracted as components of predominant powers. Thus, neural activity derived from the respiratory center of the pontomedullary networks may be difficult to detect as BOLD-related neural activity because a series of mechanical and physiological respiratory functions always have the same or concomitant rate and patterns for respiratory neuron-based activity. Based on the denoising approach, it is reasonable to explain that respiration-timing–dependent fMRI signal might not reflect rhythmic respiratory activity itself; instead, EI transition–dependent signal represents neural activity that is accompanied by PreBötC activity or neural activity that projects to modulate PreBötC activity during the task.

4.3 Respiration-dependent signaling pathways to the cerebral cortex

Our findings have thus far shown that the decline in cognitive performance was specific to the EI transition–dependent effect that the retrieval process irregularly spanned the EI transition (EI condition). While an extensive array of frontoparietal regions were activated during the encoding, delay, and retrieval processes in the DMTS task (Figure 4, Nakamura et al. 2022), the EI condition during retrieval reduced activation in the anterior cluster of the right temporoparietal junction (TPJa), right middle frontal gyrus (MFG), and left and right dorsomedial prefrontal cortex (dmPFC, containing the dorsal part of the ACC) compared to other respiratory conditions during the retrieval process (i.e., IE condition, INS condition, and EXP condition; Figure 4b, left panel in Figure 4d). However, activation in these regions during the EI condition was still higher than activation during the encoding process or the delay period of the task (right panel in Figure 4d). Our results suggested that the coordination between the timing of respiration and specific cortical networks could be a key driver in modulating brain function, thereby influencing subsequent task performance (Nakamura et al. 2022).

Here, we address the question of whether the signals generated by the respiratory center of the pontomedullary networks are transmitted to the TPJa, MFG, and dmPFC via specific neural hubs. There are several candidate hubs: the parafacial zone (Anaclet and Fuller 2017), C1 neurons (Stornetta and Guyenet 2018), PBN (Fuller et al. 2011), locus coeruleus (LC; Yackle et al. 2017), olfactory bulb (Tort et al. 2018), and thalamus (Yang and Feldman 2018). Whereas recent review articles introduced the olfactory bulb-dependent pathway (Boyadzhieva and Kayhan 2021; Maric et al. 2020), we discuss other possible pathways of respiration-dependent modulation to the large-scale brain

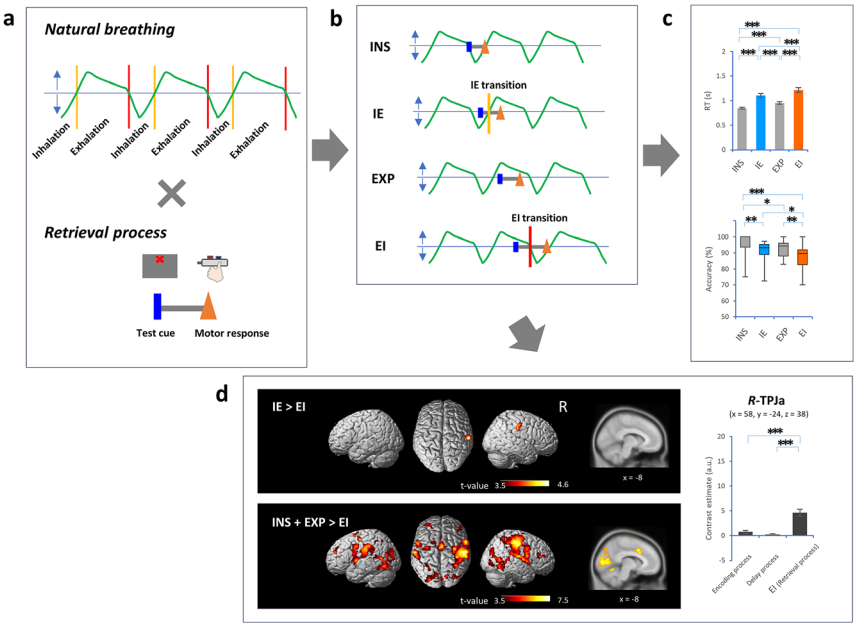

Figure 4: Respiration-timing–dependent modulation of neural substrates during the retrieval process. (a) In healthy volunteers performing the DMTS task, the retrieval process occurred during natural breathing. The retrieval process was defined by the period from a test cue to a motor response. (b) There were four conditions of crossing between natural breathing and the retrieval process: (i) the retrieval process fitting within inhalation (INS condition), (ii) the retrieval process encompassing the IE transition (IE condition), (iii) the retrieval process fitting within exhalation (EXP condition), and (iv) the retrieval process encompassing the EI transition (EI condition). (c) Plots showing that the EI condition exhibited the longest RT and lowest accuracy in the respiratory conditions. (d) Images showing brain regions that exhibited fMRI activity in the IE condition in contrast to the EI condition (IE > EI, left upper panel). Images showing brain regions that exhibited fMRI activity in the INS + EXP condition in contrast to the EI condition (INS + EXP > EI, left lower panel). Plots showing a contrast estimate in the right TPJa (MNI coordinates: $x = 58$, $y = -24$, $z = 38$, see Nakamura et al. 2022). fMRI activity was exhibited in the region of interest at an SPM{t} threshold of $p < 0.05$ with cluster-level FWE correction for the whole brain. a.u.: arbitrary unit.

networks: (i) the parafacial–PBN–basal forebrain (BF) pathway, (ii) respiration-sympathetic coupling derived by the C1 neurons, and (iii) PreBötC-LC pathway.

4.4 The parafacial–parabrachial nucleus (PBN)–basal forebrain (BF) pathway

While the parafacial respiratory group is conditionally the expiratory rhythm generator (Onimaru and Homma 2003), GABAergic neurons in the parafacial zone, which is located the dorsolateral to the facial nucleus, suppress PBN and BF activities during wakeful and sleep states (Anaclet and Fuller 2017). Cell-specific lesions of the parafacial zone resulted in insomnia, and the majority of sleep-active parafacial neurons were GABAergic/glycinergic. Then, targeted genetic disruption of GABAergic/glycinergic transmission from the parafacial zone resulted in large and sustained increases in wakefulness (Anaclet et al. 2012). GABAergic parafacial neurons monosynaptically inhibit PBN neurons that, in turn, innervate and release synaptic glutamate onto cortically projecting neurons of the wake-promoting BF, which is the primary cholinergic nuclei projecting onto the cerebral cortex (Anaclet et al. 2014, 2015). Since the PreBötC and parafacial nucleus have contrasting synaptic regulations during the respiratory cycle, it is likely that GABAergic parafacial neurons might be the primary source of EI transition–dependent modulation that inhibits glutamatergic PBN neurons and deactivates the BF and subsequent hippocampal and cortical neurons.

The PBN is considered a sensory and integrative hub for many behaviors, pain, affective states, and autonomic responses. Regarding respiratory function, the PBN, including the KFN, regulates the IE transition, expiratory airflow patterns via the control of upper airway patency, and respiratory reflexes (Arthurs et al. 2023; Dutschmann and Dick 2012; Varga et al. 2021). Fuller et al. (2011) found that glutamatergic PBN neurons have afferent projections to the BF. Lesions of the PBN or BF decreased arousal levels and caused the extensive loss of EEG power above the frequency of 1 Hz, whereas lesions of extensive thalamus had little effect on EEG and arousal levels. Moreover,

chemogenetic activation of the PBN potently drives cortical arousal and behavioral wakes via the basal forebrain and lateral hypothalamus, but not the thalamus (Qiu et al. 2016). The PBN is a key region of convergence for ascending pathways that function as a general alarm system, mediating behavioral and emotional responses to threats (Chiang et al. 2019; Palmiter 2018).

4.5 Respiration-sympathetic coupling derived by the C1 neurons

The adrenergic C1 neurons, which contain an enzyme converting noradrenaline to adrenaline phenylethanolamine N-methyl transferase, are found in the ventrolateral medulla, which has overlapping segments from the Bötzinger complex to PreBötC, to rostral ventral respiratory group (Guyenet et al. 2013; Stornetta and Guyenet 2018). The C1 neurons play a crucial role in regulating sympathetic tone, monitoring blood pressure, and stimulating the hypothalamic–pituitary–adrenal axis in circumstances such as pain, hypoxia, and hypotension (Souza et al. 2022). For example, an upright posture disinhibits the C1 neurons that directly innervate the sympathetic preganglionic vasomotor neurons, thus increasing vasomotor tone to prevent a drop in blood pressure. Menuet et al. (2017) demonstrated that C1 neuronal hyperactivity contributes to the increase in respiration-sympathetic coupling (or inspiration-sympathetic coupling) associated with diseases such as hypertension. While the C1 neurons may have direct excitatory drive from PreBötC neurons (Menuet et al. 2017), they may oppositely activate PreBötC neurons (Malheiros-Lima et al. 2018). Moreover, PreBötC neurons drive respiratory modulation of blood pressure and heart rate (i.e., RSA, Menuet et al. 2020). The C1 neurons have many afferent projections to the paraventricular nucleus and dorsomedial nucleus in the hypothalamus, and dorsal raphe nucleus, NTS, lateral PBN, and LC (Guyenet et al. 2013; Guyenet and Stornetta 2022). It cannot be ruled out the possibility that inspiration-sympathetic coupling caused by the adrenergic C1 neurons contributes to EI transition–dependent modulation and spread-out interoceptive signals to a variety of brain regions.

4.6 The PreBötzinger complex (PreBötC)–locus coeruleus (LC) pathway

The possibility that signals from the PreBötC modulate the LC was suggested by genome-wide association and molecular biological approaches. Yackle et al. (2017) showed that Cdh9/Dbx1 double-expressing PreBötC neurons had efferent projections specifically to the LC. Then, conditional, bilateral genetic ablation of Cdh9/Dbx1-expressing PreBötC neurons in adult mice left breathing intact but increased calm behavior and decreased time in arousal states, suggesting that the PreBötC regulates noradrenergic neurons in the LC and attentional states (Yackle et al. 2017).

Our findings suggest that respiratory modulation could be relevant to attention mechanisms based on the pathway during retrieval. The LC is implicated in attention and arousal (Poe et al. 2020; Sara and Bouret 2012) and has two modes of activity (Aston-Jones and Cohen 2005): phasic-mode activity that corresponds to task engagement (or exploitation) with high performance and enhances cortical activity of salience information (Vazey et al. 2018) and tonic-mode activity that is associated with the absence of phasic activity and task disengagement (or exploration). Although it remains unclear whether PreBötC-to-LC–dependent effects cause memory decline and deactivation of the right TPJa, studying patients with posttraumatic stress disorder (PTSD) may provide insights into the functional relationship of LC activity during cognitive processes (Morris et al. 2020). Normally, LC activity slows down during the state of rapid eye movement (REM) sleep and is also silent in the seconds immediately preceding sleep spindles during non-REM sleep. Furthermore, the characteristic sleep disturbance of PTSD, insomnia, and opiate withdrawal suggest overactivity of the LC during sleep, which may underlie emotional and hippocampal memory consolidation deficits in patients with these disorders (Poe et al. 2020). Importantly, PTSD patients have increased heart rates, skin conductance, eye blink, and fMRI activation in the LC and right intraparietal sulcus in response to loud sounds compared with trauma-exposed controls (Naegeli et al. 2018). These ideas propose that decreasing LC activity may be relevant to resetting the novelty of information processing and then immediately triggering consolidation (and reconsolidation).

4.7 Inferior parietal lobule (IPL)/temporoparietal junction (TPJ)

We found that the EI transition primarily reduced fMRI activation in the region that lies anatomically along the boundary between the IPL and TPJ (Nakamura et al. 2022). According to Mars et al. (2012) and Igelstrom et al. (2015), this region is classified as the right TPJa (MNI coordinates: $x = 58$, $y = -24$, $z = 38$). The right TPJa is well known as a neural core of the VAN, together with the right MFG as another neural core, which is a bottom-up system involved

in attention and awareness of surprising or salient events from the external environment (Asplund et al. 2010; Corbetta et al. 2008; Corbetta and Shulman 2002). The right MFG might be linked to the dorsal attention network, which may be involved in top-down attentional control. Furthermore, resting-state fMRI studies have shown that the right TPJa has preferential functional connectivity to the CON (also known as the salience network or SN), whose neural hubs are the dorsal part of the ACC and anterior insula, which may be involved in alertness and salience detection (Igelström and Graziano 2017; Menon and Uddin 2010). These functional connectivity studies support the idea that the VAN and CON/SN serve as macroscopic anatomical substrates to cross-link functional networks and share information (Figure 5a, Igelström and Graziano 2017; Uddin et al. 2019; van den Heuvel and Sporns 2013; Yeo et al. 2011).

Human studies have also suggested that the TPJ is one of the most prominent sources of P300 (P3) components, which are event-related potentials with a latency of 300–400 ms (Nieuwenhuis et al. 2005). P300 components are associated with surprising events (Mars et al. 2008) and are hypothesized to reflect the updating of information in anticipation of subsequent information processing (Geng and Vossel 2013; Nieuwenhuis et al. 2005). Chiefly, P300 components are assumed to reflect the phasic-mode activity of the LC (Aston-Jones and Cohen 2005; Nieuwenhuis et al. 2011). One human pharmacological study showed that while oddball target responses induced P300 components in the left and right TPJ and prefrontal cortex, these P300 components were abolished by an injection of the beta-adrenergic blocker propranolol (Strange and Dolan 2007). Interestingly, a resting-state fMRI study revealed LC-to-right TPJ functional connectivity (Liebe et al. 2020). Liebe et al. (2022) demonstrated that patients with mild cognitive impairment (MCI) had reduced LC-to-right TPJ functional connectivity but elevated LC-to-ACC connectivity and LC-to-left anterior insula connectivity. Moreover, LC-to-right TPJ connectivity was positively correlated with memory scores in dementia patients, supporting our findings that showed a positive correlation at the within-individual level between the discriminability score for memory and right TPJa activation among the respiratory conditions (i.e., the INS + EXP, IE, and EI conditions; Figure 5b, Nakamura et al. 2022). Liebe et al. (2022) suggested that an increase in LC-to-ACC, LC-to-anterior insula, and SN connectivity might result in elevated tonic-mode activity of the LC (Aston-Jones and Cohen 2005), whereas a decrease in LC-to-right TPJ connectivity could be correlated with decreased phasic-mode activity of the LC (Corbetta et al. 2008).

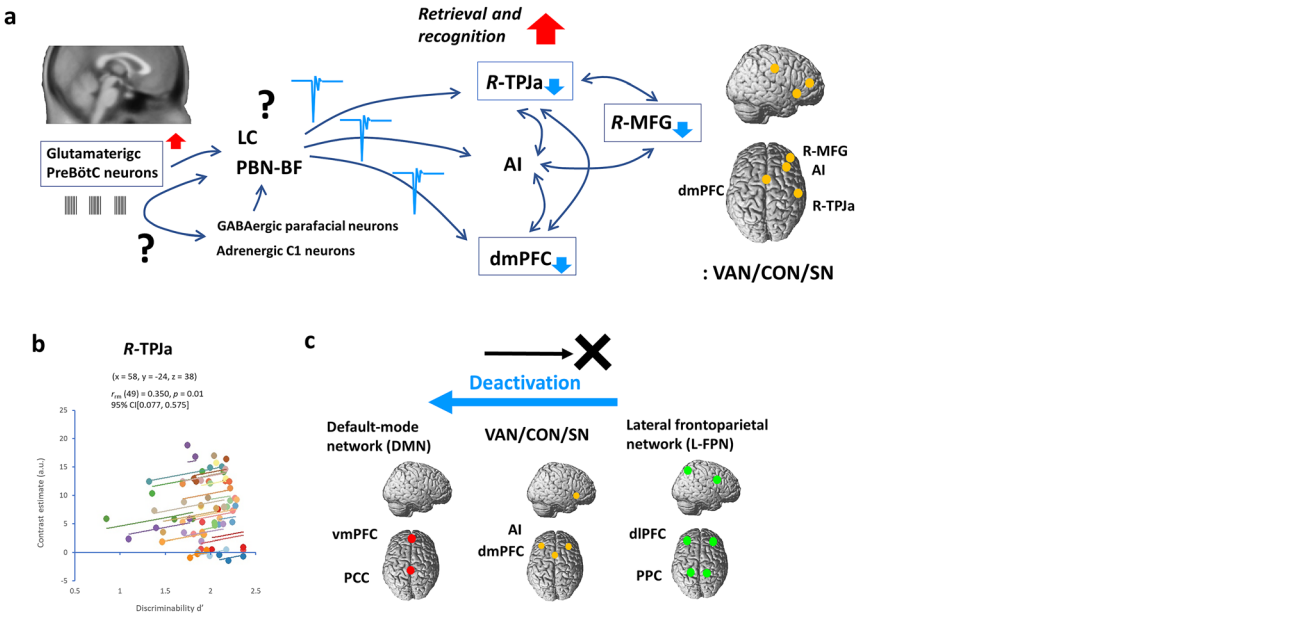

Figure 5: A potential role of the VAN/CON/SN stimulated by the EI transition. (a) Drawing showing EI transition–dependent modulation of the retrieval and recognition processes through potential pathways from the glutamatergic PreBötC neruons, GABAergic parafacial neurons, and adrenergic C1 neurons to the locus coeruleus (LC) and parabrachial nucleus (PBN)–basal forebrain (BF) to the ventral attention network/cingulo-opercular network/salience network (VAN/CON/SN). (b) Plots showing a positive correlation at the within-individual level (rmcorr) between the discriminability d' of familiarity-based memory and contrast estimates among the respiratory conditions (i.e., the INS + EXP, IE, and EI conditions) in the right TPJa (Nakamura et al. 2022). (c) Drawing showing deactivation of the VAN/CON/SN that might induce switching from lateral frontoparietal (or central executive) network activity to default-mode network (DMN) activity.

4.8 Roles of the ventral attention network (VAN)/cingulo-opercular network (CON)/salience network (SN)

At this stage, the role of the EI transition that reduced activation of the VAN/CON/SN and caused cognitive decline and decreased accuracy of the task remains puzzling (Figure 5a, Nakamura et al. 2022). However, recent findings have given significant consideration to interactions between mental health problems and functional neural networks. The SN is known as a network hub that may receive interoceptive information for an adaptive response, wherein the SN disengages the DMN and engages the lateral frontoparietal (or central executive) network in mediating attention, working memory, and other cognitive processes for goal-oriented behavior (Menon 2011; Menon and Uddin 2010; Seeley et al. 2007). Salience processing provides a motivational context for a stimulus and may thus be central to initiating motivated or resetting behavior. Conversely, aberrant salience processing may underlie motivational disturbances (Yuen et al. 2014). In humans, dysfunction and/or hyperactivity of the SN are implicated in psychiatric disorders (Goodkind et al. 2015; Peters et al. 2016), such as depression (Brakowski et al. 2017; Yuen et al. 2014), schizophrenia (Manoliu et al. 2014; Nekovarova et al. 2014), PTSD (Akiki et al. 2017; O'Doherty et al. 2015), and traumatic brain injury (Sharp et al. 2014; Scheibel 2017). Therefore, we propose that normalization of respiratory properties using breathing manipulation, e.g., rhythmic inhalation and exhalation in synchronization with sensory detection and motor responses, could be a target in mental health care to reduce or eliminate symptoms in patients with stress responses and neuropsychiatric disorders.

According to a combination of functional networks and salience processing, we hypothesized that EI transition–dependent signals may deactivate the nodes of the right TPJa, right MFG, and dmPFC (i.e., VAN/CON/SN), leading to the opposite direction of salient stimuli that might recruit the DMN switched or initiated from the lateral frontoparietal (or central executive) network (Figure 5c). Additionally, there is another modulation for "brain–breath" interactions, respiration-DMN coupling at a lower frequency (<0.1 Hz; Noble and Hochman 2019). Voluntary breathing techniques at a lower frequency are beneficial to induce behavioral relaxation and adapt physiological and brain states to the DMN. A state of respiration-DMN coupling using the breathing exercises before the task might support an efficient switch into the DMN when the retrieval process spans the EI transition. This could be a potential reason healthy volunteers could not temporally update or access information that is usually available in their memory, resulting in extended RT and unsuccessful retrieval (Nakamura et al. 2022, 2018). This idea may also be relevant to the results that the timing of button-press responses for cognitive processes was tightly distributed ahead of the EI transition (Nakamura et al. 2022), suggesting that participants may involuntarily avoid passing through the EI transition during retrieval due to the difficulty in answering correctly. Elucidation of the detailed functional relevance of breathing to large-scale brain network activity with different task demands is a subject for future work.

5 Conclusions

It is considered that neural network activity during cognitive processes can be coordinated with the respiratory cycle and these processes might be constantly updated during online brain states. However, cognitive processes are significantly extended or incongruous when they span the EI transition, resulting in failed performance. Emerging evidence assumes that the EI transition might reset novelty processing (i.e., encoding and retrieval) and then immediately trigger consolidation (and reconsolidation). This perspective suggests that the EI transition may play an important role of a "reset and trigger" whose related neural substrates may be incorporated in the VAN/CON/SN. Thus, stimulation of these functional networks by breathing manipulation could be applied to improve dysfunction, abnormal activity, and/or hyperactivation of the SN in patients with stress responses and neuropsychiatric disorders. These considerations of brain–breath interactions would contribute to a better understanding of interoceptive and cognitive mechanisms that underlie brain–body interactions in health conditions and in neuropsychiatric disorders.

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