

Coupling of respiration and attention via the locus coeruleus: Effects of meditation and pranayama

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Abstract

The locus coeruleus (LC) has established functions in both attention and respiration. Good attentional performance requires optimal levels of tonic LC activity, and must be matched to task consistently. LC neurons are chemosensitive, causing respiratory phrenic nerve firing to increase frequency with higher CO₂ levels, and as CO₂ level varies with the phase of respiration, tonic LC activity should exhibit fluctuations at respiratory frequency. Top-down modulation of tonic LC activity from brain areas involved in attentional regulation, intended to optimize LC firing to suit task requirements, may have respiratory consequences as well, as increases in LC activity influence phrenic nerve firing. We hypothesize that, due to the physiological and functional overlaps of attentional and respiratory functions of the LC, this small neuromodulatory nucleus is ideally situated to act as a mechanism of synchronization between respiratory and attentional systems, giving rise to a low-amplitude oscillation that enables attentional flexibility, but may also contribute to unintended destabilization of attention. Meditative and pranayama practices result in attentional, emotional, and physiological enhancements that may be partially due to the LC's pivotal role as the nexus in this coupled system. We present original findings of synchronization between respiration and LC activity (via fMRI and pupil dilation) and provide evidence of a relationship between respiratory phase modulation and attentional performance. We also present a mathematical dynamical systems model of respiratory-LC-attentional coupling, review candidate neurophysiological mechanisms of changes in coupling dynamics, and discuss implications for attentional theory, meditation, and pranayama, and possible therapeutic applications.

KEYWORDS

attention, coupling, meditation, pranayama, respiration, synchronization

1 | INTRODUCTION

Chale vāte chalam chittam nischale nischalam bhavet

Yoghī sthānūtvamāpnoti tato vāyūm nirodhayet

Respiration, being disturbed, the mind becomes Disturbed. By restraining respiration, the Yogi gets Steadiness of mind.

Hatha Yoga Pradapika, Yogi Svatmaram

Yogis and Buddhist practitioners have long considered the breath an especially suitable object for meditation. The choice of the breath over other possible items arose presumably not simply because respiration provides a subtle and readily available object of focus, but because the characteristics of respiration can be observed to change in specific ways with attentional and emotional states. It is believed that by observing the breath, and regulating it in precise ways—a practice known as pranayama—changes in arousal, attention,

and emotional control that can be of great benefit to the mediator are realized. Innumerable anecdotal reports support these claims, and physical, emotional, and attentional improvements have been noted in many studies (reviews: Chiesa, Calati, & Serretti, 2011; Grossman, Niemann, Schmidt, & Walach, 2004; Lippelt, Hommel, & Colzato, 2014; Sengupta, 2012).

We know from behavioral and imaging studies that meditative practices are associated with improvements that activate and strengthen the frontal attentional system (Hölzel et al., 2011; Lazar et al., 2005; Luders, Toa, Leport, & Gaser, 2009; Vestergaard-Poulsen et al., 2009) and that default mode network (DMN) activity, associated with mind-wandering states, is reduced (Brewer et al., 2011; Taylor et al., 2013; Wells et al., 2013). Changes in cortical volume and white matter connectivity have also been observed (Laner et al., 2015; Luders, Clark, Narr, & Toga, 2011; Tang et al., 2010; Tang, Lu, Fan, Yang, & Posner, 2012) even following short periods of practice. Meditation and pranayama also produce changes in respiration (Vyas & Dikshit, 2002; Wallace & Benson, 1972) and autonomic nervous system activity, as measured by habituation, frequency, and spontaneous galvanic skin response (GSR) response to stressors (Orme-Johnson, 1973) and cardiorespiratory coupling (Cysarz & Bussing, 2005).

One might suppose that the object of focus in meditation should be irrelevant, that it is the act of focusing attention and not the object of focus—in this case, the breath—that is important. But the Buddha states clearly, in the *Ananda Sutra*: “from the development, from the repeated practice, of respiration-mindfulness concentration, there comes to be neither wavering nor trembling of body, nor wavering nor trembling of mind” (Sai, 2010). According to Svatmarama, in the *Hatha Yoga Pradapika* (2:2), “. . .when the breath wanders the mind is unsteady. But when the breath is calmed, the mind too will be still” (Muktibodhananda, 2013). Patanjali, in the *Yoga Sutras* (2.53), instructs that “. . . through these practices and processes of pranayama, which is the fourth of the eight steps, the mind acquires or develops the fitness, qualification, or capability for true concentration (dharana). . .” (Satchidananda, 2012). The focus upon the breath is of clear importance in traditional practice, but how might respiration and attention influence each other from a neurophysiological perspective?

While a few scattered scientific attempts at examining the relationship between respiration and attention have been made (Gellhorn & Kraines, 1936; Lehmann, 1893; Porges & Raskin, 1969; Taylor, 1901; Winkler, 1898), a comprehensive theory and concrete neurobiological mechanism that can explain the effects of respiratory monitoring and control on cognition, and vice versa, has not been proposed. One interesting possibility is that the respiratory and attentional systems are coupled at the neural level, such that information

transfer between the two systems occurs bidirectionally at an anatomical point where the respiratory and attentional systems overlap.

In this review, we describe respiration and attention as a coupled dynamical system. Specifically, we hypothesize that they can be described as autonomous oscillatory systems exhibiting coupling via information transfer through a third autonomous oscillator, the locus coeruleus (LC). We review the neurophysiological knowledge of the relevant systems, emphasize the influence of CO₂ on LC tonic activity, the importance of LC activity to attentional state and stability, and discuss how these may be synchronized with top-down influences from attentional areas.

1.1 | Coupled systems

Coupling, or synchronization, is a common phenomenon in nature, particularly in biological systems. Weakly interactive forces (e.g., mechanical vibrations, heat, or sound) cause autonomously oscillating systems to tend toward a synchronized state (Huygens, 1673; Pikovsky, Rosenblum, & Kurths, 2001; Strogatz & Stewart, 1993).

This phenomenon was first described by Huygens after he lay sick in bed on a long sea journey, observing two pendulum clocks hanging upon a common wooden beam. He noted the gradual synchronization of the pendula, and eventually discovered that very small vibrations were passing between clocks, through the beam upon which they were fixed, causing the pendula to drift into, and then remain, permanently fixed, in one of two states—either perfect synchronization or antisynchronization (a stable phase relationship of 180°).

As it turns out, examples of this type of synchronized behavior are common in the natural world (e.g., flashing fireflies, flocks of birds in flight, slime mold behavior), and synchronization is thought to play an important role in neural and physiological systems as well. Neural systems exhibit phase and frequency synchronization (Buszaki & Draguhn, 2004), both between larger functional areas (Engel & Konig, 1991; Konig, Engel, Lowel, & Singer, 1993) and individual proximal neurons (Gray, Koenig, Engel, & Singer, 1989). Neuronal coupling is thought to subservise perceptual binding (Eckhorn, Reitboeck, Arndt, & Dicke, 1988; Gray et al., 1989), cortical communication and coordination (Fries, 2005), and influence attention and saliency (Biedlack et al., 2006). Nonlinear physiological coupling between the heart and respiration in human beings has also been observed (Jamsek, Stefanovska, & McClintock, 2004; Schafer, Rosenblum, Kurths, & Hans-Henning, 1998). It is important to point out that synchronization in the context of dynamical systems is the result of independently oscillating systems interacting and tending toward stable interdynamics in the absence of external forcing or entrainment.

1.2 | LC and cognition

In mammals, the LC, a small blue bilateral nucleus in the pons, is the main source of cortical noradrenaline (NA), and through a nearly complete and exclusive innervation of the cortex (Loughlin, Foote, & Bloom, 1986), plays a significant role in regulating brain function. The LC can be loosely considered a cortical analogue of the adrenal glands, influencing arousal and helping optimize cognitive states for varied environmental and volitional demands.

NA is a modulatory neurotransmitter, known to be involved in regulating sleep-waking states (Aston-Jones & Bloom, 1981; Jones, 1991), cortical arousal (Carter et al., 2010), signal detection threshold (Sara & Hervé-Minvielle, 1995; Segal & Bloom, 1976; Waterhouse, Moises, & Woodward, 1998), and decision processes (Aston-Jones, Rajkowski, & Kubiak, 1997; Bouret & Sara, 2004; Clayton, Rajkowski, Cohen, & Aston-Jones, 2004; Rajkowski, Majczynski, Clayton, & Aston Jones, 2004; Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999). The LC exhibits a continuum of behavior, ranging from high sustained tonic firing during episodes of distractibility (Aston-Jones, Rajkowski, & Cohen, 1999; Aston-Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996; Usher et al., 1999) to near-absolute, GABA-inhibited quiescence during REM (rapid eye movement) sleep (Aston-Jones & Bloom, 1981).

While the role of the LC in waking and arousal has long been known, a recent focus on its specific cognitive and attentional functions has revealed two distinct modes of firing that are associated with equally distinct modes of attentional strategy (Aston-Jones & Cohen, 2005). Projections from the orbitofrontal cortex (OFA) and anterior cingulate (ACC) are thought to drive the LC-noradrenergic (LC-NA) system into one of two stable states of activity, a high tonic (sustained) mode or a phasic (bursting) mode accompanied by moderate tonic activity (Aston-Jones & Cohen, 2005). The OFA and ACC are known to play a role in calculating task utility, and there are prominent efferent connections to the LC from both (Aston-Jones et al., 2002; Rajkowski, Lu, Zhu, Cohen, & Aston-Jones, 2000; Zhu, Iba, Rajkowski, & Aston-Jones, 2004), with few sparse connections from other cortical areas.

The switching of attentional state via tonic LC activity theoretically results in a flexible attentional system that allows cycling between exploitative and exploratory behaviors to find and meet task demands in a changing environment, and is known as the adaptive gain theory (Aston-Jones & Cohen, 2005). In brief, during exploitative behavior, when an agent is focused on a singular task with high perceived utility, high-amplitude transient phasic bursting is observed preceding behavioral responses to task-relevant stimuli, sustained firing is maintained at a moderate level, and task performance is relatively strong. As task utility wanes, and tonic

LC firing increases, phasic firing is reduced. This level of tonic LC activity facilitates a decoupling of attention from the current object of focus, which allows a reevaluation of the current environments (both mental and physical) and the generation of hypotheses, goals, and subgoals of potentially greater value (Hayes & Petrov, 2015).

Attention is also known to exhibit regular oscillations between task-focused and mind-wandering states (Fox & Raichle, 2007; Franson, 2006; Songua-Barke & Castellanos, 2007), which would necessitate, according to the adaptive gain theory, a corresponding oscillation in LC tonic activity that temporarily broadens the focus of awareness, by increasing neural gain and functional connectivity (Eldar, Cohen, & Niv, 2013). The mechanism responsible for this oscillation is believed to be a metabolic process (Songua-Barke & Castellanos, 2007), but remains unknown. This “refresh cycle” of attention essentially opens an opportunistic window for attentional reallocation and is thought to be periodic, with a frequency somewhat greater than 0.1 Hz (Langner & Eickhoff, 2013; Robertson, Ridgeway, Greenfield, & Parr, 1997).

1.3 | LC and CO₂ chemosensitivity

While the cognitive and attentional aspects of LC activity are interesting and impressive on their own, the LC simultaneously carries out a second phylogenetically more primitive role, as an important part of the brainstem respiratory network. It is well established that brainstem respiratory nuclei initiate respiration when intracellular or extracellular CO₂ levels increase. LC neurons exhibit chemosensitivity to hypercapnic states (Gargaglioni, 2010), increasing inspiratory drive when CO₂ (H⁺)¹ levels are increased (Biancardi, Bicego, Almeida, & Gargaglioni, 2008; Filosa, Dean, & Putnam, 2002; Gargaglioni, Hartzler, & Putnam, 2010; Oyamada, Ballantyne, Muckenhoff, & Scheid, 1998; Pineda & Aghajanian, 1997). In vitro LC neurons have been shown to fire in synchrony with the respiratory phrenic nerve (Oyamada et al., 1998), and increased LC firing frequency of up to 126% has been observed with controlled decrease in pH levels in the LC (Filosa et al., 2002). Chemical ablation of LC neurons results in a significant attenuation of the hypercapnic respiratory effect (Biancardi et al., 2008; Noronha-de-Souza et al., 2006). Connections from the LC to preinspiratory neurons have also been identified (Dobbins & Feldman, 1994; Yackle et al., 2017). Importantly, because arterial CO₂ levels are known to fluctuate with respiration (Band, Cameron, & Semple, 1969; Band, Wolff, Ward, Cochrane, & Prior, 1980; Honda & Ueda, 1961; see Figure 1), this should induce a corresponding fluctuation of LC tonic

¹Positive hydrogen ions result from CO₂ combining with H₂O to produce carbonic acid, which is then broken down into bicarbonate, resulting in a surplus H⁺ ion.

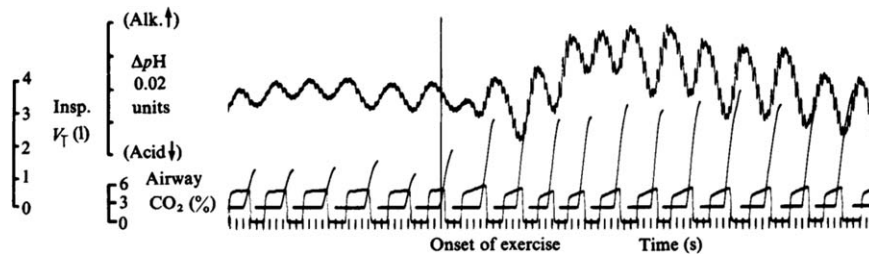


FIGURE 1 Oscillation of $\text{CO}_2(\text{pH})$ at respiratory frequency (from Band et al., 1980; reprinted with permission)

activity at the same frequency, as these chemosensitive neurons are bathed in arterial blood.

1.4 | LC and meditation

Given the wide-ranging influence that the LC has on attention, respiration, and autonomic activity, it is unsurprising that it has been hypothesized to play an important role in the effects of meditation. Craigmyle (2013) theorizes that via activation by the ACC, which is a part of the salience, orienting, and executive attention networks (Peterson & Posner 2012; Posner & Petersen, 1990), the LC adapts the cortical and peripheral nervous systems of the organism to optimize behavior to a constantly changing environment, and that meditation improves the individual's ability to do this. Importantly, cortical NA has been directly observed to decrease during meditation (Infante et al., 2001; Walton, Pugh, Gelderloos, & Macrae, 1995), and increased gray matter density in the pons (the location of the LC and other important respiratory nuclei) has been found in a cross-section of long-term breath-focused meditators (Vestergaard-Poulsen et al., 2009), as well as in a randomized study (Holzel et al., 2011).

1.5 | LC as respiratory-attentional coupling mechanism

The LC is obviously an interesting candidate as a potential coupling mechanism in a hypothetical respiratory-attentional system, as it has important simultaneous roles in both attention and respiration. Consisting of approximately 25,000 neurons per hemisphere, this small nucleus could offer important insights into attentional dynamics and play an important role in an empirical explanation of the ancient insights of yogis and meditators. It could also potentially explain some of the cognitive and emotional benefits observed with various breath-centered practices by helping to explain how respiration and attention are linked (Figure 2).

2 | INITIAL RESEARCH FINDINGS

Recent research from our lab has revealed that LC activity, as measured by BOLD imaging and pupil dilation, a known

proxy of LC activity (Joshi, Kalwani, & Gold, 2016; Murphy, O'Connell, O'Sullivan, Robertson, & Balsters, 2014; Murphy, Robertson, Balsters, & O'Connell, 2011; Rajkowski, Kubiak, & Aston-Jones, 1993), exhibits phase coherence, or is synchronized, with respiration (Figure 3).

In brief, respiration, pupil dilation, and BOLD activation were measured in 14 individuals during an 8-min resting scan and a 20-min auditory oddball task (see Murphy et al., 2014). Stimulus presentation during the task was pseudorandom with an interstimulus interval of 2.5–3.5 s. A pupil-covariant subset of LC neurons was isolated, and corrected for instantaneous physiological noise (RETROICOR). Covariance with activity in the fourth ventricle, an area proximal to the LC and known to exhibit significant respiratory artifacts during MRI, was also regressed from the LC time series to control for physiological respiratory artifacts.

To examine respiratory-related LC activity, normalized LC BOLD signals were locked to the instant of the peak and trough of respiration (± 8 s), and vector averaging was performed. Task LC activation showed clear synchronization with respiratory phase (Figure 3a), and an apparent 180° phase difference in LC BOLD activity between respiratory peak and respiratory trough was verified by cross-correlation. Paired *t* tests for dependent samples (two-tailed) showed highly significant signal separation at 4–8 s following the peak/trough of respiration (Table 1, $df = 7772$). Corresponding resting state analysis of peak versus trough locked activity showed a sustained antisynchronized pattern

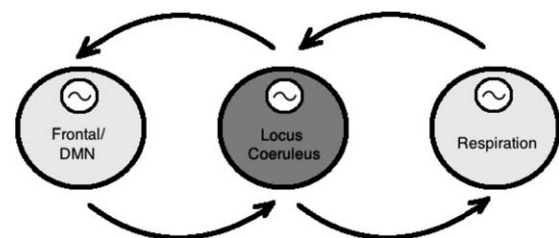


FIGURE 2 Diagram showing hypothesized coupled information transfer between respiratory and attentional systems via the LC. Frontal attentional systems influence LC tonic/phasic activity. Oscillation of CO_2 levels cause tonic fluctuations in LC at respiratory frequency. LC tonic activity in turn influences both attentional state and respiration. Note the bidirectionality of the coupling. Such coupled systems tend to evolve toward stable, nonlinear, or chaotic synchrony. Sine wave inside of circle indicates autonomously oscillating system

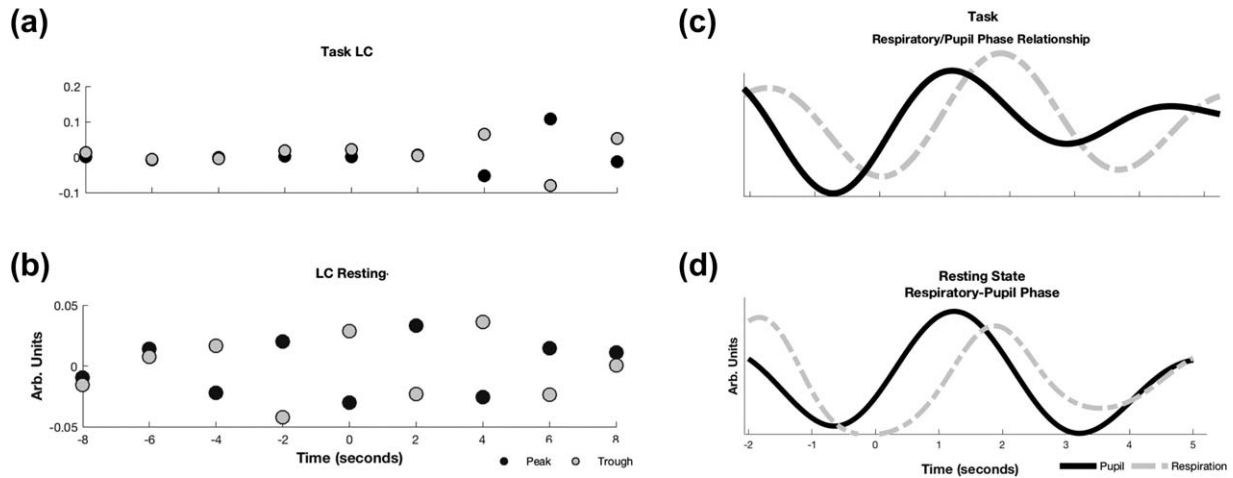


FIGURE 3 (a) Respiratory-locked LC activity (respiratory peak vs. trough) during oddball task session. (b) Respiratory-locked LC activity (peak vs. trough) during rest. (c) Normalized pupil and respiratory global averaged waveforms during task locked to the trough of respiration. (d) Normalized pupil and respiratory global averaged waveforms from resting state locked to the trough of respiration. (c) and (d) are illustrative of respiratory-pupil synchronization and their phase offset

of activity (Figure 3b), and this was verified by cross-correlation and with a circular test for nonuniformity (R test, $df = 9,9$, $z = 7.84$, $p < .0001$) performed on the angular phase differences (calculated with Hilbert transform) of the two signals. Amplitude comparisons, however, while suggestive of a trend (Table 2, paired t tests for dependent samples, single-tailed; $df = 3358$), were not highly significant. Possible reasons for this are the shorter duration of the resting scans relative to task and the absence of task-driven phasic LC amplitude contributions.

As a supplement to the paired t tests, and to further examine the null hypothesis that LC activation did not differ between respiratory peak and trough, bootstrap tests were conducted by aggregating LC activation time-locked to each peak and trough for each time point (-8 to +8 s) and resampling vectors of the same length with replacement ($n = 50,000$). A comparison of the true mean peak-trough difference in LC activation with the bootstrapped distributions for both task and resting state produced results roughly comparable with paired t tests for both task (Table 1) and resting state (Table 2).

Because increasing evidence suggests that pupil diameter provides a noninvasive proxy of LC activity (Alnaes et al., 2014; Joshi et al., 2016; Liu, Rodenkirch, Moskowitz, Shriver, & Wang, 2017; Reimer et al., 2016; Unsworth & Robinson, 2016; Varazzani, San-Galli, Gilardeau, & Bouret, 2015), a corresponding analysis was conducted on respiratory-locked normalized, blink-corrected pupil waveforms. This revealed a clear pattern of synchronization during both task and rest (Figure 2c,d). Phase coherence, a measure of the angular difference of the instantaneous phase between two signals (Equation 1) was calculated to be $R = 0.977$, with a mean phase difference $\Delta\theta = -1.629$ radians (rad) for task and $R = 0.803$, $\Delta\theta = -1.79$ during rest. We interpret both the LC and pupil findings as suggestive of synchronization between respiratory, LC, and pupil activity.

$$R = \left| \frac{1}{N} \sum_{j=1}^N e^{i[\theta_x(t_j) - \theta_y(t_j)]} \right| \quad (1)$$

Equation 1. Method used to calculate phase coherence (R), where N is the sample size of the

TABLE 1 Task respiratory-locked LC BOLD analysis results

	Time to respiratory peak/trough								
	-8 s	-6 s	-4 s	-2 s	0 s	2 s	4 s	6 s	8 s
Paired t score	0.064	0.235	0.533	0.213	0.427	1.014	4.349	5.530	2.715
p value	.949	.814	.594	.831	.669	.314	< .0001	< .00001	.007
Bootstrap ($n = 50,000$)	.52	.592	.71	.42	.34	.16	0	0	< .005
p value									

Note. Significant antisynchronization observed from 4–8 s following respiration.

TABLE 2 Resting state respiratory-locked LC BOLD analysis results

	Time to respiratory peak/trough								
	-8 s	-6 s	-4 s	-2 s	0 s	2 s	4 s	6 s	8 s
Paired <i>t</i> score	0.094	0.115	0.976	2.002	1.923	1.620	1.403	0.892	0.1757
<i>p</i> value	.537	.454	.165	.023	.027	.053	.080	.186	.430
Bootstrap (<i>n</i> = 50,000) <i>p</i> value	.626	.555	.230	.041	.04	.056	.070	.163	.433

Note. Effects are marginal, but a trend toward significance is present.

angular distribution, $i = \sqrt{-1}$ (imaginary operator), e is the natural logarithm, and θ_x and θ_y are instantaneous phase angles (in radians) from two different signals at time t_j . R returns an average vector of length $0 \leq R \leq 1.0$. Instantaneous phase values are calculated using the Hilbert transform.

To examine how respiratory activity might be related to attentional performance, participants were binned into low and high reaction time variability groups (RTV). RTV is known to correlate well with attentional performance (Jensen, 1992) and is higher in groups with compromised attention, such as attention deficit hyperactivity disorder (ADHD; Kofler et al., 2013; Tamm et al., 2012), dementia (Hultsch et al., 2000), Alzheimer's disease (Gorus, De Raedt, Lambert, Lemper, & Mets, 2008; Jackson, Balota, Duschek, & Head, 2012; Tse, Balota, Yap, Duschek, & McCabe, 2010), and traumatic brain injury (TBI; Whyte, Polansky, Fleming, Coslett, & Cavallucci, 1995). Importantly, high RTV is present more so in TBI patients with focal frontal lesions as opposed to nonfrontal lesions (Stuss, Murphy, Binns, & Alexander, 2003). RTV also covaries with LC tonic firing rate (Usher et al., 1999) and prestimulus pupil diameter (Murphy et al., 2011; van den Brink, Murphy, & Nieuwenhuis, 2016) in simple target detection tasks.

The angular phase of respiration at the instant of stimulus presentation was calculated for all trials for all participants, and mean participant phase-locking angles were calculated. Clear clustering near the trough of respiration (-2.53 rad) was observed in the low RTV group (Figure 4a), while the HRTV group exhibited greater variability, with an advanced mean phase angle (-1.37 rad) approaching the top of the respiratory cycle. The mean phase angle difference was highly significant (Watson-Williams test, $F = 279.6$, $df = 6240$, $p < .0001$) at the individual trial level, and marginally significant at the participant level (Watson-Williams test, $F = 4.1$, $df = 1,14$, $p = .06$). Variability (concentration) of phase-locking angle was significantly different between the high and low RTV groups at both item (K test, $F = 1.095$, $df = 1,6271$, $p < .0001$) and the participant level (K test, $F = 5.98$, $df = 1,14$, $p = .02$).

2.1 | Present findings discussion

Respiration has been observed to exhibit phase synchronization to stimulus presentation in another study (Huijbers et al., 2014), and recent research (Yackle et al., 2017) has shown that removal of respiratory pattern generator (cahedrin-9) pre-Botzinger neurons reduces arousal in mice, possibly via termination of the connection from this respiratory pattern generator to the LC. A commentary on this finding further

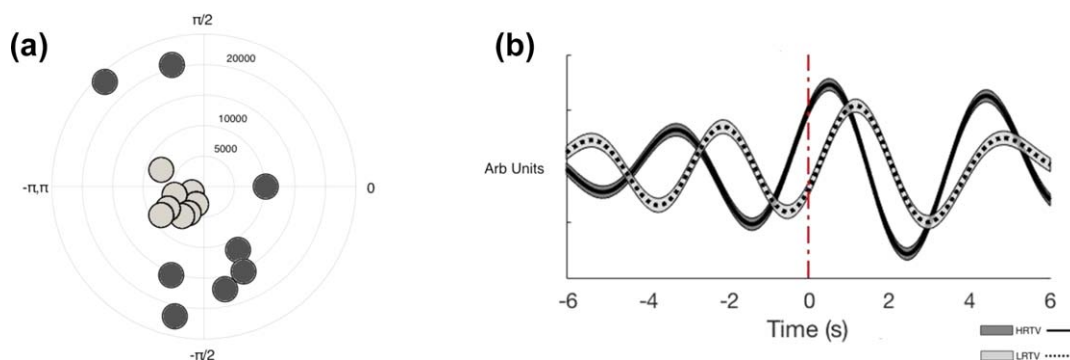


FIGURE 4 Analysis of participants binned into high and low RTV. (a) Stimulus-locked instantaneous Respiratory Phase Angle \times RTV (low vs. high groups). Participant mean stimulus-locked respiratory phases were used for clarity of presentation. RTV on radial axis. (b) Stimulus-locked respiratory waveform averaged across all trials for low and high RTV groups

suggested that respiration could affect arousal, and perhaps cognition, via the LC (Sheikhbaehi & Smith, 2017), and a very recent study has observed coupling between respiration and fluctuations of electrical activity in rodent brains (Tort, Brankack, & Draguhn, 2018). Stimulus-locked respiratory phase has further been shown to affect perception of fear and the encoding of memory (Zelano et al., 2005), and respiration exhibits coupling with frontal theta activity (Stankovski et al., 2016), which is inversely related to DMN activity (Braboszcz & Delorme, 2011; Scheeringa et al., 2008). These studies, our findings reported above, and the existing functional and anatomical knowledge of the LC and its connectivity together suggest that the respiratory and attentional systems may indeed be coupled. The lack of strong LC BOLD amplitude findings during the resting state condition above require cautious interpretation, however, and further higher powered studies would be required to decisively determine if this synchronization can be observed by direct imaging of the LC. This caveat notwithstanding, the strong LC-respiratory synchronization during task, and pupil-respiratory synchronization in both conditions, do suggest that these signals may indeed be coupled during rest as well as during an attentionally demanding exercise. The present findings also indicate an attentional advantage related to a more accurate and precise phase modulation of respiration.

3 | PROPOSED MATHEMATICAL MODEL OF RESPIRATORY-LC-ATTENTIONAL COUPLING

We outline below a model of the relationship between respiration and attention, and their hypothetical coupling via the LC. The LC, the attentional system, and respiratory activity all exhibit regular oscillations, and can be considered autonomous noisy oscillators, exhibiting weak, possibly transient, and/or nonlinear coupling (Figure 1). The dynamics of such a system can be expressed as a group of coupled differential equations. Models of this type have previously been used to describe system dynamics of neural and physiological rhythms (Mirollo & Strogatz, 1990; Pikovsky et al., 2001). Our proposed system of equations describing the coupling between respiration, attention, and LC oscillatory systems is described in Equation 2.

$$\begin{aligned}
 \dot{\phi}_A &= \omega_A + \varepsilon_A F_A(\phi_A, \phi_{LC}) + \xi_A \\
 \dot{\phi}_{LC} &= \omega_{LC} + \varepsilon_{LC} F_{LC}(\phi_{LC}, \phi_A, \phi_R) + \xi_{LC} \\
 \dot{\phi}_R &= \omega_R + \varepsilon_{LC} F_R(\phi_R, \phi_{LC}) + \xi_R
 \end{aligned} \tag{2}$$

Equation 2. Description of the coupled dynamical system of autonomous oscillators of respiration, LC tonic activity, and task-focused/DMN

oscillation (“attentional refresh cycle”), where $\dot{\phi}$ is a first order derivative describing a variable’s phase evolution with respect to time, ω is the natural frequency of the oscillator, ε is the coupling strength, F is the coupling function (a 2π -modular function), ϕ is the instantaneous phase, and ξ are stochastic, linear, or nonlinear (potentially 2π -periodic) noise terms.

There are obviously other factors, considered noise terms presently in the model, that will affect the ultimate dynamics expressed by the individual oscillators, and the coupled system as a whole, such as environmental exigencies (stimuli), autonomic influences, and other neural connections, so this “sandboxed” model can be viewed as an abstracted, idealized expression of the isolated dynamics of the hypothesized respiratory-attentional system with the LC as its nexus. It would be possible, of course, to expand the model to include other oscillatory (e.g., autonomic fluctuations) and pulsatile (e.g., environmental stimuli) influences.

A similar mathematical description was employed recently by Stankovski et al. (2016) to examine the effect of anesthesia on coupling dynamics of heart rate, respiration, and frontal EEG signal, in which they observed coupling between respiration and frontal theta rhythm. As mentioned, frontal theta amplitude is a negatively correlated index of DMN activity, which is active during task-unrelated thought, or mind wandering, so this finding is of direct relevance to our hypothesis.

The present model also shares similarities with mathematical models for schizophrenia in which shallower basins of attraction and decreased attractor stability lead to decreased memory and increased distractibility (Loh, Rolls, & Deco, 2007; Rolls, Loh, Deco, & Winterer, 2008), and differences in phase-locking dynamics and coupling strength of the auditory cortex and thalamus contribute to changes in auditory evoked potentials (Popovych, Kupper, Muller, & Brockhaus-Dumke, 2009; Rosjat, Daun-Gruhn, & Popovych, 2014).

3.1 | Proposed modulators of respiratory-LC-attentional coupling

As we theorize not only that these systems are coupled, but also that breath-focused practices can alter the nature of this coupling, we speculate below on five possible mechanisms by which the coupling strengths (ε) and noise terms (ξ) in the above equations might be modulated, thereby modifying the dynamics of the coupling between respiration and attention.

3.1.1 | Attentional and executive systems

As mentioned earlier, meditation is associated with functional, electrical, morphometric, and connective changes in the brain, indicative of increased frontal control (see Tang,

Holzel, & Posner, 2015, for a review), along with decreased oscillation between mind-wandering and focused states. The ACC, an integral part of the attentional system, is known to directly modulate LC activity (Craigmyle, 2013; Sara & Herve-Minvielle, 1995). While there have been no direct recording studies of LC activity in meditators, increased attentional stability, a known result of meditative practices (Lutz, Slagter, Dunne, & Davidson, 2008; Jha, Krompinger, & Baime (2007); Slagter et al., 2007) should logically be accompanied by stabilized tonic modulation of the LC. It is worth reiterating here that our preliminary data show that natural variation in attentional performance (RTV) dissociates the indices of LC function; therefore, it follows that meditation should further flatten the tonic dynamics of the LC.

3.1.2 | Insula and interoceptive feedback

The insula is known to incorporate visceral information about the physiological organism (Craig, 2002), and its activity has been shown to correlate with the ability to consciously monitor physiological processes (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004), including respiration (Daubenmier, 2013; Farb, Segal, & Anderson, 2012, 2013). Research on the morphology and activity of the insula in meditators shows overall increased volume and activity (Holzel et al., 2007; Lazar et al., 2005; Manna et al., 2010; but see Luders et al., 2009), and increased gyrification (Luders et al., 2012). Decoupling of the insula and DMN also occurs in trained meditators relative to controls (Farb et al., 2007). This makes sense, as most types of meditation and pranayama involve paying strict attention to respiration and other visceral sensations, and reducing mind wandering and distractive thoughts.

This increased sensitivity to physical sensations, particularly of ongoing respiratory activity, resulting from the augmented activation and morphology outlined above, could play an important role in neural changes that allow for more precise predictive targeting of tonic LC phase angle and amplitude. More specifically, it is possible that insular changes could alter coupling between respiration and attention by improving signal transmission of respiratory activity back to the cortex, allowing more effective synchronization of respiration to task.

3.1.3 | Autonomic regulation

The autonomic nervous system maintains the balance of arousal, matching sympathetic and parasympathetic influences with internal and external demands (Thayer & Lane, 2000). The LC plays a complementary cognitive role to the autonomic arousal systems. This is necessary for effective behavior, and an inability to appropriately balance cortical and peripheral arousal can be observed in persons with ADHD (Anderson et al., 2000; Nagai, Cavanna, & Critchley, 2009; Satterfield & Dawson, 1971).

In general, LC activity increases sympathetic activity and decreases parasympathetic activity via its projections to the spinal cord and various autonomic nuclei. Parasympathetic influence is reduced via inhibitory projections to the vagal nuclei, while the excitatory effect of the LC on sympathetic activity is more complex, involving combinations of excitatory and inhibitory projections. For an in-depth treatment of this complex subject, see Samuels and Szabadi (2008).

Meditation and pranayama are known to alter the sympathetic-parasympathetic balance of the nervous system (Bhargava, Gogate, & Mascarenhas, 1988; Ditto, Eclache, & Goldman, 2006; Fundeburke, 1977; Stancak, Kuna, Srinivasan, & Dostalek, 1991; Takahashi et al., 2005; Tang et al., 2009; Telles et al., 2013; Wallace, 1970), as indicated by changes in heart rate, heart rate variability, respiration frequency and depth, blood pressure, and galvanic skin response. Pranayama has been observed to alter this balance toward sympathetic or parasympathetic activation depending on the method practiced (Rhaguraj, Ramakrishnan, Nagnendra, & Telles, 1998), and focused states are associated with increased autonomic stability (Porges, 1992; Porges & Raskin, 1969). It has been hypothesized that these changes are due to stretch-receptor induced vagal inhibition resulting from deep respiration (Jerath, Edry, Barnes, & Jerath, 2006).

It is possible that some of the beneficial effects of meditation are mediated by altered autonomic functioning and via the LC, given its intimate relationship to arousal.

3.1.4 | CO₂ sensitivity

Because LC activity is known to vary with CO₂, it is important to consider not only the level of blood CO₂ but also the sensitivity of the organism to it. There is evidence that CO₂ is reduced during meditation (Wallace & Benson, 1972; Wolkove, Kreisman, Darragh, Cohen, & Frank, 1984), and studies also suggest that CO₂ sensitivity in the respiratory centers of the brainstem is decreased with prolonged practice of pranayama (Joshi et al., 1992; Miyamura et al., 2002; Stanescu, Nemery, Veriter, & Marechal, 1981). If true, this could cause a reduction in the amplitude and variability of the LC oscillation at respiratory frequency. While it is not known if the LC specifically is affected in this way, a reduction in LC tonic variability could increase attentional settling into a stable attentional attractor state, thereby making unintentional attentional shifts due to chemosensitive (CO₂) fluctuations less likely.

The evidence for CO₂ sensitivity from pranayama studies is supported by research on deep-sea divers (Earing, McKeon, & Kubis, 2014; Florio, Morrison, & Butt, 1979; Froeb, 1961) and people living at extremely high altitudes (Chiodi, 1957), all of whom show habituation to elevated levels of CO₂. Interestingly, people suffering from anxiety-related disorders show an increased sensitivity and an

inability to habituate to high CO₂ levels (Blechert et al., 2010).

3.1.5 | Possible interaction of vagal and CO₂ influences

It is well established that LC neurons are chemosensitive to fluctuating CO₂ levels, and should therefore result in an oscillation of LC tonic activity at respiratory frequency. Vagal activity also modulates LC tonic discharge (Groves & Brown, 2005). This fact is exploited in vagal nerve stimulation (VNS), which increases LC activity (Fornai, Ruffoli, Giorgi, & Paparelli, 2011; Svensson & Thoren, 1979; Takigawa & Mogenson, 1977), and is used therapeutically to suppress seizures and treat drug-resistant depression (Groves & Brown, 2005). This effect is both immediate (Groves & Brown, 2005) and has been observed to last up to 3 days following treatment (Dorr & Debonnel, 2006). Lesioning and inactivation of the LC block the seizure-attenuating effects of VNS (Krahl, Clark, Smith, & Browning, 1998). The exact mechanism of action for this is not known, but is thought to possibly involve the nucleus of the solitary tract (NTS), as the area is richly innervated by vagal fibers (Groves, Bowman, & Brown, 2005).

It has been suggested by several authors that stretch receptors in the lungs inhibit vagal input to the LC, possibly via the NTS. This would hypothetically result in a second sinusoidal oscillation of tonic LC activity at respiratory frequency. Pulmonary vagal fibers terminate in the NTS (Kubin, Alheid, Zuperku, & McCrimmon, 2006), and the cardiovascular area of the NTS has an established efferent pathway to the peri-LC (Van Bokstaele, Peoples, & Telegan, 1999), which in turn innervates the LC proper (Aston-Jones, Zhu, & Card, 2004; Jin et al., 2016). Physiological inhibition of the LC via the vagus nerve has also been shown to occur following controlled baroreceptor (blood pressure) loading (Elam, Svensson, & Thoren, 1985; Elam, Yoa, Svensson, & Thoren, 1984; Murase, Inui, & Nosaka, 1994). There are, however, presently no direct stimulation studies in the literature showing that respiratory vagal information is relayed to the LC, so this remains a speculative, though intriguing, idea. We note this as a possible significant contribution to respiratory-attentional coupling, but remain keenly aware that this is hypothetical until definitive direct stimulation studies have been performed.

3.2 | Illustration of modulation of model coupling dynamics

According to our proposed model, any change in a system parameter will have global results upon the dynamics of the entire system. To illustrate this concept more clearly, we examine here dynamical changes in an extremely simple

case where only respiratory frequency is modulated. We chose this parameter because decreased respiratory frequency, as low as one breath per minute for an hour (Miyamura et al., 2002), is an established effect of pranayama practice (Joshi, Joshi, & Gokhale, 1992; Pinheiro, Medeiros, Piinheiro, & Marinho, 2007), and also because respiratory dynamics play a fundamental role in our theory.

As can be seen in Figure 4, the three-dimensional stable attractor states of the coupled systems exhibit qualitative changes in response to modulation of respiratory frequency (ϕ_R). As respiratory frequency is decreased, the resulting limit cycle becomes increasingly stable or tightly coupled,² the plane of the attractor changes, and the resulting attentional oscillation decreases in frequency, as do its magnitude and slope (Figure 5b). The frequency and slope magnitude changes observed in the model suggest corresponding frequency and slope changes in the underlying attentional refresh cycle. Changes of this sort could be of benefit for stabilizing attention to task due to dilated periods of stable LC tonic activity, reduced frequency and amplitude of attentional oscillations, and decreased unintended mind-wandering interruptions.

4 | DISCUSSION

Given our knowledge of the involvement of the LC in attention, cognition, and arousal, its susceptibility to top-down control, its concurrent chemosensitive respiratory function, and the possible respiratory-induced vagal influence on LC firing, we hypothesize that the LC is a critical node in facilitating coupling between respiration and attentional state. It is important to stress that this coupling is bidirectional. Craigmyle (2013) has articulated that the LC, via ACC activation, is likely an integral contributor to the beneficial effects of breath-centered practices on arousal and attention. By introducing bottom-up respiratory influences on the LC into this picture, we can then imagine the LC as a nexus of information transfer between these two systems, and visualize the system as bidirectionally coupled (Figure 2).

As previously mentioned, the human attentional system exhibits regular fluctuations between a task-positive network and the DMN, associated with task-focused and mind-wandering states, respectively. Likewise, respiration exhibits regular oscillations that are normally highly dependent on CO₂ levels in the brainstem. With breath-focused practice, respiration decreases in frequency, as does the frequency of mind

²It is possible to quantify the variability of the coupled systems by their Lyapunov exponents (Rosenstein, Collins, & De Luca, 1993; Wolf, Swift, Swinney, & Vastano, 1985) and approximate entropy (Pincus, 1991), which are measures of the divergence and complexity of the system, respectively, but we refrain from doing so here as we wish solely to describe the model in general terms.

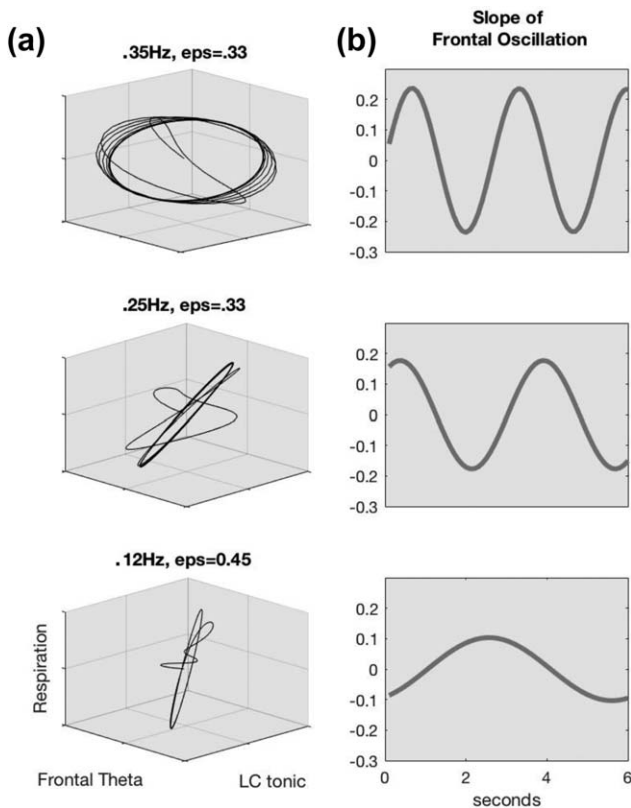


FIGURE 5 Phase space plots derived from Equation 2. (a) Left hand column shows limit cycle attractors at three different respiratory frequencies (.35 Hz, .25 Hz, .12 Hz). Note changes in variability and orientation of attractor in phase space. Coupling coefficient (epsilon) required to achieve stability was identical at .35 Hz and .25 Hz, but noticeably higher for slowest respiratory frequency (.12 Hz), possibly suggestive of increased connectivity requirements. (b) Resulting slope of estimated frontal (attentional) oscillation. Frequency of attentional oscillation decreases with decreasing respiratory frequency, suggestive of decelerated and attenuated attentional refresh cycle component underlying attentional stability

wandering (Brewer et al., 2011; Mrazek, Franklin, Phillips, Baird, & Schooler, 2013), with an increased ability to remain in a focused state. A decoupling of attention is characterized by increased LC tonic activity and subsequent increase in neural gain and functional connectivity, allowing a temporary competition for attentional resources. Given the known effect magnitude of CO_2/pH on tonic LC activity, it is possible that respiratory-induced LC fluctuations could provide a window of attentional flexibility, or a refresh cycle, to a single attentional system that must address task demands, internal hypothesis generation, and external exigencies by nimbly alternating between them as appropriately and as efficiently as possible.

Sources of noise in LC activity, such as fluctuating arousal levels, CO_2 sensitivity, and possibly poor vagal tone, are attenuated by meditation practice. This attenuation could reduce the amount of frontal input or effort necessary to maintain attentional state on task, and reduce the probability of unintended attentional shifting due to fluctuations in neural gain and functional connectivity. In fact, it has been noted

that meditators of intermediate experience ($\sim 19,000$ hr) show increased activation in attentional areas compared to novices or nonmeditators, but extremely advanced meditators ($\sim 44,000$ hr) show lower activation in those areas than all groups (Brefczynski-Lewis, Lutz, Schaefer, Levinson, & Davidson, 2007). Interviews confirmed this: after a prolonged period of practice, very little effort is required to maintain attention in a conscious focused state. The stabilization of attentional states by reducing and/or adapting to the respiratory influences on LC tonic variability in long-term practitioners could be one contributing factor.

We propose that the coupled respiratory-LC-attentional system can be described as a dynamical system consisting of three coupled autonomous oscillators, which can be characterized by a stable three-dimensional attractor in phase space. In this model, the attentional network maintains stable states due to its own internal dynamics, and shifts between these states can occur by either inhibitory processes (e.g., frontal input), energy dissipation (e.g., waning task utility or fatigue), or novel injections of energy into the system (e.g., environmental urgency or altered CO_2/pH levels). Evolution of the internal dynamics of this system, resulting from breath-focused meditation and pranayama, could influence the stability and/or depth of these attractor basins, lowering the requirements of energy needed to maintain attentional states and decreasing the frequency of unintended attentional shifting (Figure 6).

It is important to point out that there is a fundamental difference between mindfulness practices in which the breath is passively monitored with no effort to control it, and pranayama practices, where the breath is actively regulated. Simple observation of the breath is an extremely challenging vigilance task, and practice will likely improve attentional function, and affect

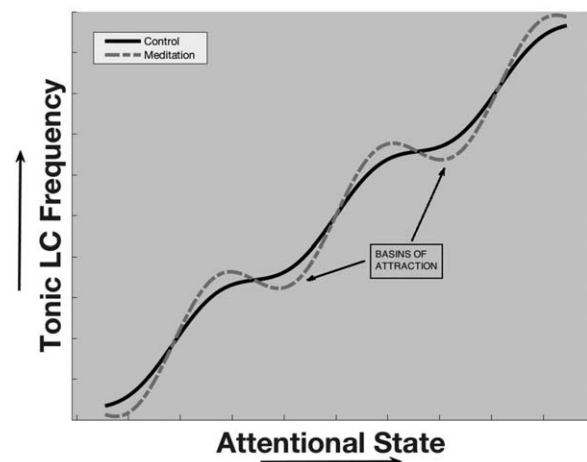


FIGURE 6 Abstract representation of hypothetical attentional basins of attraction and tonic LC activity in meditators versus controls. As system dynamics change (e.g., coupling function increases), the depth and stability of attractor states hypothetically increase, requiring less energy input to sustain and resulting in a lower probability of unintended attentional shifting

LC tonic activity, via strengthening of the frontoparietal attentional system, including the insula and the ACC. Such monitoring tasks would therefore improve ability to target appropriate adjustments of LC activity, and possibly to fine-tune respiratory phase angle predominantly in a top-down way; however, it is unlikely that they would have as large an effect on bottom-up mechanisms of physiological regulation of LC function. Pranayama and other breath control practices, on the other hand, should reduce respiratory frequency, modulate arousal, improve vagal tone, and reduce CO₂ sensitivity, and so most of the resulting benefits should be physiologically derived. There will likely be some overlap in these general categorizations, as merely observing the breath will undoubtedly alter it to an extent, and breath regulation will improve focused attention to a degree. Classifying breath-centric practices in this way, however, could prove useful in targeting practices in a therapeutic sense, and aid in understanding the specific effects of different breath-centered practices.

The hypotheses that respiration and attention comprise a coupled system via the LC, and that breath-focused practices will alter its dynamics, have the potential to increase our understanding of the attentional system and how it interacts with physiological processes such as respiration. We have briefly summarized the current understanding of the LC as it relates to both attention and respiration, and described several mechanisms that could be involved in the coupling dynamics of this system, and their possible evolution through these practices. This could open a window into a deeper scientific understanding of the cognitive benefits of breath-centered practices, and possibly offer a scientific explanation as to why the breath may offer an ideal object of focus for meditation. Research on this hypothesis could further result in non-pharmacological therapeutic possibilities for attentionally compromised populations (such as ADHD, TBI, and elderly populations), with different practices targeting specific problems with either maintenance of physiological states of arousal or frontal control mechanisms.

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