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More than a rhythm of life: Breathing as a binder of orofacial sensation

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Abstract

When rodents engage in the exploration of novel stimuli, breathing occurs at an accelerated rate that is synchronous with whisking. We review the recently observed relationships between breathing and the sensations of smell and vibrissa-based touch. We consider the hypothesis that the breathing rhythm serves not only as a motor drive signal but also as a common clock that binds these two senses into a common percept. This possibility may be extended to include taste through the coordination of licking with breathing. The status of experimental evidence that pertains to this hypothesis is evaluated.

The cycle-by-cycle control of breathing originates in the preBötzinger complex, a cluster of neurons whose rhythmic output initiates every breath (reviewed in references 1 and 2) and thereby provides the motor drive to sample odors (Fig. 1a,b). Axons from the preBötzinger complex project to neuronal centers that are involved in the patterning of latter phases of breathing[1–3], as well as to neuronal oscillators that are presynaptic to the orofacial motoneurons that drive whisking[4] and licking[5,6]; the case for chewing is equivocal[7]. The relatively tight spatial organization of these orofacial oscillators in the intermediate reticular zone of the medulla may provide a means for rapid interactions, which at the very least are necessary to preserve patency of the upper airway[8] (Fig. 1b). Here we examine the possibility that the breathing rhythm, in addition to its physiological role in homeostasis, may serve a perceptual role in the binding of orofacial sensory inputs that enter through the pons, medulla, and olfactory bulb (Fig. 1c). This is not unlike the hypothesis that concerns the binding of thalamocortical signals, where a high-frequency γ-rhythm serves as a reference oscillation to align disparate sensory inputs[9,10].

The relation of olfactory signaling to the breathing cycle was noted by Adrian[11] over 70 years ago. More contemporary work with rats by Cury and Uchida showed that this

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This prospective is dedicated to the late John C. Curtis.

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relationship holds for all behaviorally-relevant frequencies of breathing[12] and, further, Uchida and Mainen showed that perception of odorants is tightly coupled to the breathing cycle[13]. As a means to determine if rodents code olfactory signals relative to a peripheral reafferent signal, *i.e.*, a reference signal that is derived from sensation of the airflow, as opposed to an efferent copy of the respiratory drive, Sobel and Tank[14] tracheotomized animals so that they breathed at their basal rate while the nasal airflow was modulated at an incommensurate frequency. These authors observed that neurons in the olfactory bulb indeed spiked in phase with the modulation in nasal airflow. This implies that a reafferent signal, as opposed to an efference copy of breathing, is used as a reference signal. There are two likely origins of the peripheral reafferent signal. First, Wallois and colleagues[15] showed that primary trigeminal neurons that innervate the nasal cavity are activated in phase with breathing. Second, Ma and colleagues[16] showed that the local field potential in the olfactory bulb of mice, a measure of population activity, synchronizes with the pattern of breathing. This response is lost when olfactory receptors are genetically silenced. Thus the trigeminal signal may act as a reafferent signal to the olfactory cortex, but not the olfactory bulb, for which the olfactory receptors appear to supply their own reafferent signal. In summary, while breathing provides the active drive for olfaction, the motor reference for coding olfactory signals is derived by peripheral reafference as opposed to an ascending projection from premotor respiratory neurons in the medulla (Fig. 1a,b).

Exceptional detail regarding neuronal responses in the olfactory bulb of mice is provided in a recent study by Shusterman, Smear, Koulakov and Rinberg[17]. These investigators recorded spikes from mitral cells in the olfactory bulb from alert head-fixed mice in response to the addition of odorants to an airstream presented to the animal (Fig. 2a). As expected from past work, the spiking patterns of neurons in the olfactory bulb varied from odor presentation-to-presentation, as shown by the example in Figure 2b. However, when the spiking responses are aligned to the onset of the subsequent inspiration and, further, the time-base is warped to an average breath cycle, the response for this example cell is observed to be tightly locked to sniffing (Fig. 2c). These investigators further demonstrated that, as a population, different mitral cells below the same glomerulus preferentially spike at different phases in the breath cycle (Fig. 2d); this observation is consistent with the intermingling of mitral cells with input from different glomeruli[18], yet is surprising given the rapid kinetics of agonist binding to olfactory receptor neurons[19]. While it is unclear from this study whether the observed phase differences are invariant to changes in respiratory tidal volume or odorant concentration[19], or the frequency of sniffing[20], additional work from Rinberg and colleagues[21] addressed the behavioral relevance of mitral cell activation within the breath cycle. Here, these investigators showed that mice were able to report the saliency of sham odorants induced by optogenetic activation of mitral cells in terms of the phase of activation within the breathing cycle. This occurred with a relatively high accuracy of 0.4 radians. Together these physiological and behavioral results support the computational relevance of coding of olfactory stimuli in terms of phase in the breath cycle.

In an analysis similar to that in the olfactory bulb (Fig. 2), the relation of the spike rate of neurons in olfactory cortex relative to the onset of inspiration is provided in a recent study by Miura, Mainen and Uchida[22]. The spike rate of neurons in this cortical area are observed

to be locked to the onset of inspiration. These data show that the phase-dependence of neurons in the olfactory pathway is preserved through the level of projection neurons in the olfactory cortex.

We now consider a complementary orofacial behavior in rodents, vibrissa-based touch. Contact of an object by an individual vibrissa is known to induce spiking activity in primary sensory cortex during exploratory whisking[23], with the strongest responses in layers 4 and 5a[23,24]. Further, behavioral experiments have established that rodents can report touch as a function of the position of their vibrissae[25–27], consistent with a reafferent signaling of the phase of vibrissa position. Does the motion of the vibrissae influence the spike rate, similar to the way breathing influences the spike rate code of neurons in olfaction? We first consider the reference signal for vibrissa position, analogous to the signal for air flow in breathing (Fig. 2a). The spike rates of units in the trigeminal ganglion, the principal vibrissa sensory nucleus in thalamus and, of most relevance, primary vibrissa sensory cortex of rats and mice show unimodal tuning to position in the whisk cycle as rats actively explore the space around their head prior to contact with an object (summarized in reference 28). Specifically, about half of the units throughout the depth of cortex have a spike rate that is significantly modulated by whisking[23]. The origin of this sensitivity to position is unclear, but may rely on the distribution of forces on stretch receptors in the follicle[29,30]. The phase component of the position signal, found by warping the period of each whisking cycle and discarding the amplitude and midpoint of the whisk[28], was found to be derived from peripheral reafference[31,32]. Further, the spike rate of different units peak at different phases[28]. Thus spiking as a function of position in the whisk cycle provides a reference signal based on physical motion, similar to the case of reafference based on air flow in olfaction[15,16].

The preferred phase for spiking by different cortical units was revealed in an assay of active sensing[23] (Fig. 3a), in which rats were trained to rhythmically whisk in search of a contact sensor for a food reward. The design of this assay ensured that contact with the sensor occurred across of a wide range of positions, and all phases, in the whisk cycle. A plot of the spike rate for units in primary vibrissa sensory cortex upon contact as a function of angle in the whisk cycle shows an absence of tuning, as seen in the example of Figure 3b, *i.e.*, absolute position does not affect spiking. In contrast, a plot of the spike rate for the same unit as a function of phase in the whisk cycle shows strong tuning (Fig. 3c). These data imply that although the amplitude and midpoint of whisking slowly varies across whisks, the cortical spiking responses are normalized to the particular region scanned by the rat. Lastly, as a population, units with different preferred phases of vibrissa contact preferentially spike at corresponding phases in the whisk cycle (Fig. 3c). All phases are represented, with a bias toward a phase of π radians or retraction from the protracted angle. Thus, current physiological and behavioral evidence is consistent with the hypothesis that the coding of touch in terms of phase in the whisking cycle is computationally relevant for the animal.

The results of the aforementioned experiments for smell and vibrissa-based touch in rodents show that both senses are locked to self-generated oscillatory movements: breathing for olfaction (Fig. 2) and whisking for touch (Fig. 3). Are there behaviors in which these oscillatory movements are phase-locked? Indeed, synchronization of whisking with breathing in the aroused rat was noted by Welker[33] over 50 years ago. Yet the detailed

timing, state-dependence, and mechanism of this synchrony were clarified only recently. In particular, rhythmic whisking is controlled by a neuronal oscillator in the ventral medulla whose phase is reset by the inspiratory drive signal for breathing[4]. Thus, to the extent that animals are vigorously whisking and sniffing, the two rhythms are robustly phase-locked on a cycle-by-cycle basis[4,34]. By combining the phase-dependent responses in sensory cortex during sniffing and whisking, we estimate that a substantial fraction of units in the olfactory cortex[22] that respond to odors may spike in synchrony with units in vibrissa cortex that report touch[23] (teal and red bars, Fig. 4b). A similar conclusion is reached when we express the phase response for units in the olfactory bulb in terms of the their expected presynaptic activity at the olfactory cortex[17], *i.e.*, correcting for the propagation and synaptic delays from the olfactory bulb to cortex[35] (green bars, Fig. 4b). We emphasize that these comparisons are crude yet useful, especially as phase-locking as opposed to synchrony *per se* is the essential issue.

The observation of precise phase-locking between sniffing and exploratory whisking leads to the hypothesis that the breathing rhythm functions as the reference oscillation for the alignment of commensurate signals. For example, when rodents are actively exploring their environment, phase locking between whisking and sniffing could ensure that spikes induced by tactile and olfactory stimuli occur with a fixed temporal relationship to one another, which corresponds to an object with a particular smell at a particular location relative to the face. Furthermore, the observed phase-locking between sniffing and head-bobbing[33] may similarly allow the animal to compute the location of the combined sensory percept relative to the body and thereby aid in spatial navigation. This provides a means to bind inputs from smell, which enter the brain at its rostral pole, with coincident inputs from touch, which enter the brain at the level of the brainstem (Fig. 4c). It obviates the need for a direct neuronal projection of respiratory output between these two regions. This scheme may be readily extended to taste through the entrainment of licking[5] and thus covers the full range of stimuli required to assess the shape, odor, texture, and taste of food. It is of interest to explore the yet unresolved behavioral manifestations of phase-locking among the motor drives for the different orofacial senses.

Coincident detection of sensory signals relayed along independent pathways forms the essential computation in temporal binding. What is the neuronal basis for such detection? Neurons readily function as robust detectors of coincident depolarizing input and, further, can function of detectors of phase-locked but not synchronous depolarizing inputs through the use of active dendritic processes[36]. The situation for neurons with mixed excitatory and inhibitory inputs, which is particularly relevant for cortical neurons[37], is somewhat more complicated. When excitatory and inhibitory inputs are balanced, such that inward and outward currents cancel each other on average, temporal coincidence among the inputs to a neuron can lead to a high level of variability in the membrane potential. So long as the inputs are not so strong as to substantially increase the conductance of the cell, synchronous inputs are transformed into an increase is spiking rate[38]. Thus the overlap of the phase response curves for sniffing and breathing (Fig. 4b) could serve to enhance the downstream read-out of phase-locked activity.

Is phase-sensitive detection the only route to decode and bind sensory input? The answer is likely to be no. A recent study addressed the possibility of coding tactile object location based on spike count alone[39]. Optogenetic activation of neurons in vibrissa primary sensory cortex was used as a replacement of vibrissa tactile sensory input, analogous to the aforementioned optogenetic activation of mitral cells at different phases in the breathing cycle[21]. Specifically, mice were trained to report the location of a pole placed either near to or far from the resting position of a vibrissa. Contact with the pole at the near position led to a relatively high spike rate for neurons in primary vibrissa sensory cortex, compared to a relatively low rate for contact at the far position. On some trials, optogenetic stimulation of cortical neurons concurrent with different vibrissa positions was used to create the percept of illusory contact with a pole. On these trials, the mice indicated the presence of a pole regardless of vibrissa position. This suggests that the timing of touch-induced spikes relative to position was insufficient to infer location, and supports coding of contact at different angles in terms of the ensemble spike count in primary sensory cortex[39]. However, throughout the task the mice chose to scan only a relatively narrow range of angles in the vicinity of the near pole, rather than the full range of potential targets[26]. Thus it is possible that coding based on spike count holds only for a motor strategy that involves minimal whisking, as opposed to large amplitude whisks during free exploration[23,26]. We conclude that rodents can use multiple schemes to code sensory input in discrimination tasks, but that phase coding remains a viable strategy during exploratory whisking.

What are the anatomical substrates for the merging of orofacial senses? A likely locus of convergence of touch and taste input with smell, and thus the hypothesized temporal binding of orofacial sensory inputs, is ventromedial prefrontal cortex. Indeed, ventromedial prefrontal cortex receives direct projections from olfactory, gustatory, and somatosensory cortical areas[40] (Fig. 4c). A second likely candidate for multimodal integration, first noted by Johnston[41] over 90 years ago, is the basolateral amygdala. This region receives direct projections from the olfactory bulb as well as projections from olfactory cortex, gustatory cortex and, via the insula, somatosensory cortex[42]. Lastly, the medial dorsal nucleus of thalamus mediates signaling from both the amygdala and the olfactory cortex to prefrontal cortex as part of a recurrent loop between prefrontal cortex and the amygdala[43]. The results of a lesion study in the medical literature highlight medial dorsal nucleus as a functional locus for the integration of orofacial stimuli[44]. These anatomical substrates provide targets for an experimental program on neuronal recording during a multimodal behavior task. One ready possibility is to record from units when animals sweep up odorants in a layer of soil as they whisk along the ground in search of sources of food.

Lastly, we recall that the θ-rhythm plays a prominent role in the formation of new memories in the hippocampus and the amygdala. Further, the frequency distribution of the θ-rhythm overlaps with that of whisking and sniffing. Although the θ-rhythm and exploratory whisking are incommensurate during stereotypic behaviors[45], one cannot exclude the possibility that sniffing, whisking, head-bobbing, and possibly tasting may transiently synchronize the θ-rhythm with respiration[46], particularly in the presence of stimuli of intense behavioral interest[47]. We suggest that such synchrony would facilitate the formation of memories that involve a confluence of orofacial senses.

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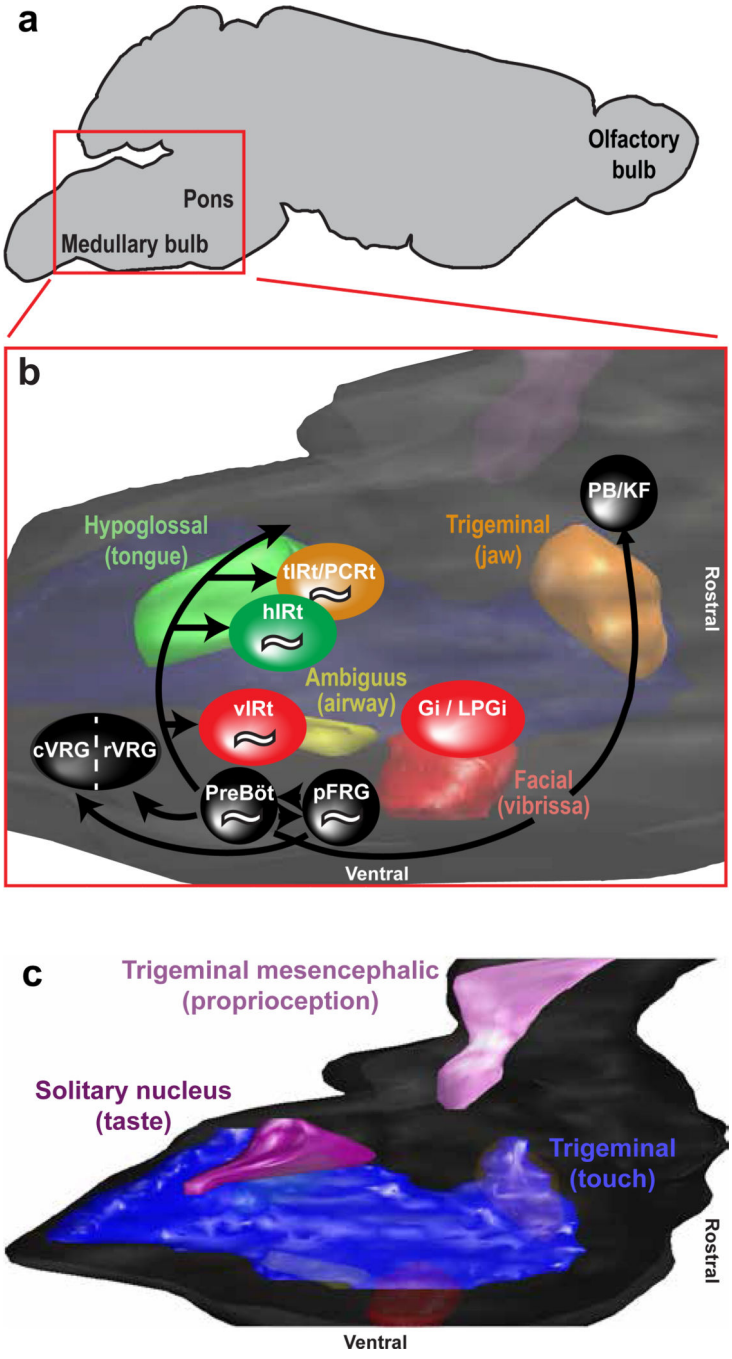

Figure 1. Brainstem circuits generate and coordinate orofacial actions and encode non-olfactory orofacial stimuli

(a) Sagittal view that shows the locus of olfactory input through the olfactory bulb at the rostral role and the locus of touch, texture, and taste orofacial input though the pons and medullary bulb. The motor areas for all of these active senses are located in the medulla. **(b)** Three-dimensional reconstruction of the medulla and pons that shows the pools of cranial motoneurons that control the jaws (orange), face and vibrissa (red), airway (yellow), and tongue (green) as background, while the approximate locations of known premotor nuclei to

each of the motoneuron pools are color coded according to the primary motor nucleus that they innervate. Breathing-related regions are shown in black. The putative neuronal oscillators that generate breathing (black), whisking (red), licking (green), and chewing (orange) are marked with a "~". Summarized from references 1, 3–5, and 48–50. Abbreviations: parvocellular reticular formation (PCRt), caudal and rostral ventral respiratory groups (cVRG and rVRG, respectively), trigeminal, hypoglossal and vibrissa intermediate reticular formation (tIRt, hIRt, and vIRt, respectively), preBötzinger complex (PreBöt), parafacial respiratory group (pFRG), gigantocellular reticular formation (Gi), lateral paragigantocellular reticular formation (LPGi), and parabrachial and Kölliker-Fuse (PB and KF, respectively). **(c)** Three-dimensional reconstruction of the medulla and pons to highlight nuclei that receive primary sensory inputs. Cutaneous inputs from the face innervate the trigeminal sensory nuclei (blue), proprioceptive innervation of the jaw muscles arises from cells in the trigeminal mesencephalic nucleus (pink), and gustatory inputs from the tongue innervate the solitary nucleus (magenta).

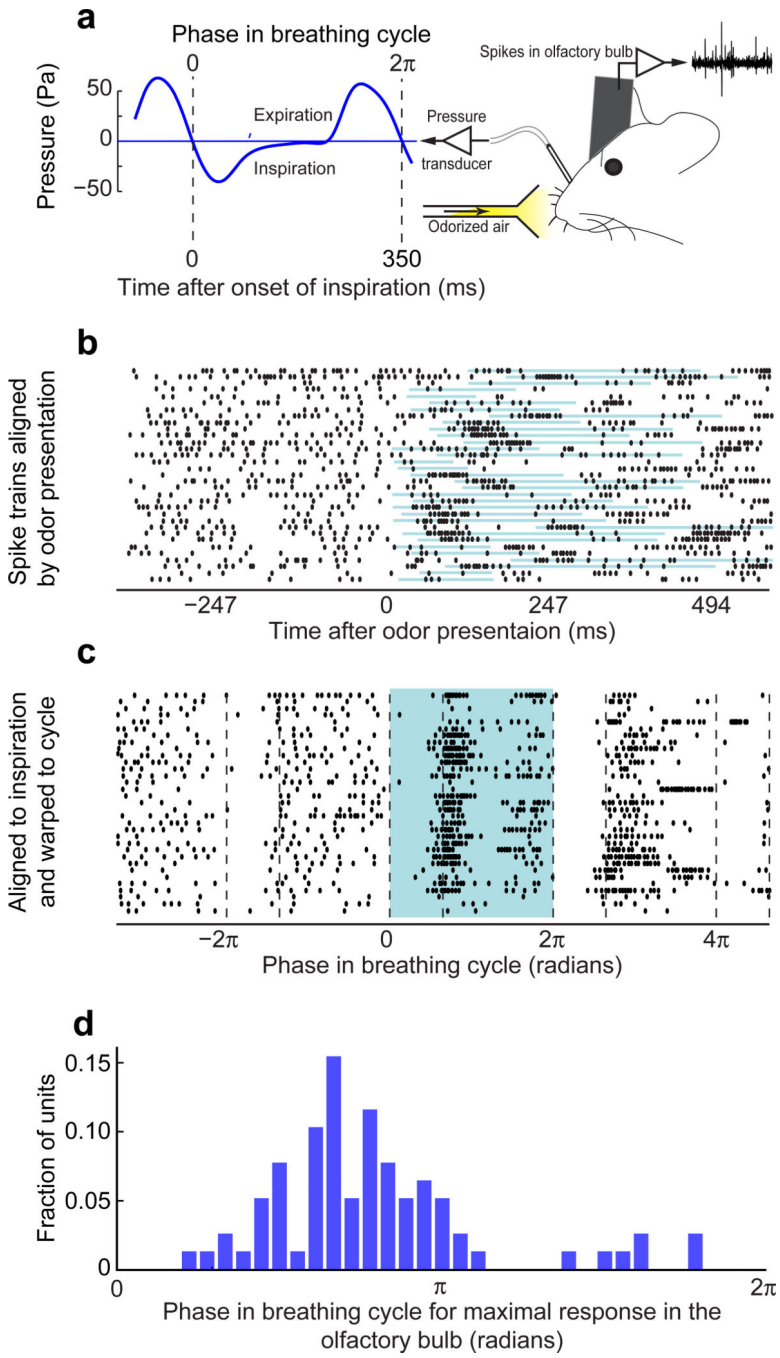

Figure 2. Smell is coded by projection neurons in the olfactory bulb whose spike rate is phase-locked to the breathing cycle

(a) An odor delivery port was positioned in front of the nose of a head-fixed mouse. The animal was implanted with an intranasal cannula to log pressure and infer breathing and a multi-wire electrode head-stage to log mitral cell extracellular spiking. The pressure waveform of a typical breathing cycle indicates the onset of inspiration. (**b**) Raster plots of spiking for an example mitral cell in response to an odor stimulus. The light blue lines underlying the raster plots indicate the duration of the first breath after odor onset (**c**) Same

raster plots as in panel b, but aligned by inspiration onset and temporally warped. The light blue lines indicate the temporally warped duration of the first sniff after odor onset and the vertical dashed lines indicate the beginning and end of inspiration intervals. (**d**) Distribution of the peak of the neuronal responses phase-shifts relative to the onset of inspiration (panel a) for a set of high signal-to-noise responses (78 out of 467 responses across 66 units in 7 mice). All panels adapted from reference 17.

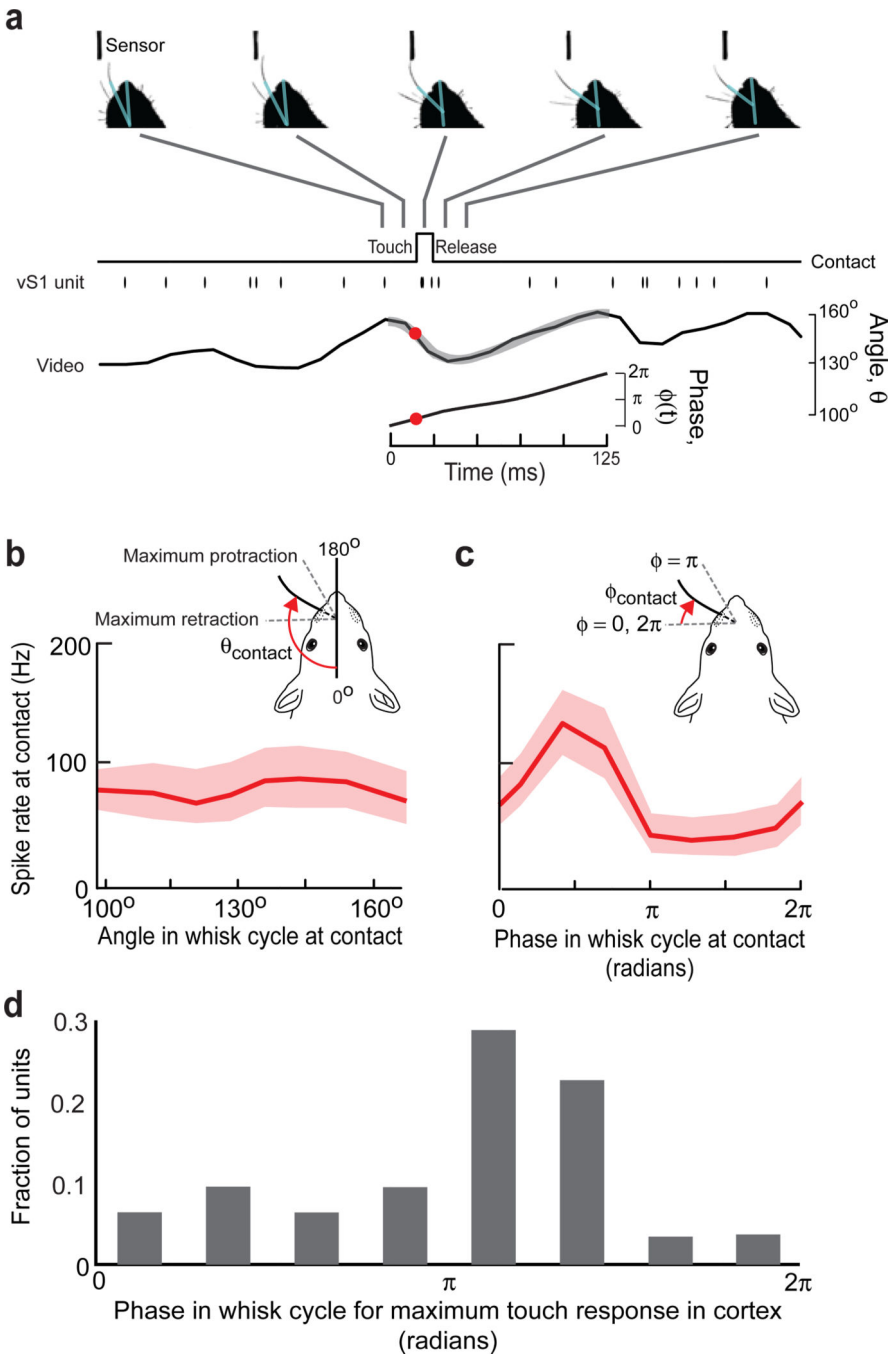

Figure 3. Vibrissa touch during exploratory whisking is coded by neurons in layer 4 and 5a of primary vibrissa cortex

(a) The rat, trimmed to single vibrissa, is held in a sock that lines a plastic tube, cranes from a perch to contact a piezoelectric touch sensor. Spike signals from multiwire-electrodes in primary vibrissa cortex, along with contact and video data on vibrissa position are logged. Example data surrounding a contact event is shown and includes vibrissa position, the fitted touch signal and accompanying video frames, and the spike times from a single units. The angle, θ(t), for the cycle with a contact event is decomposed into phase, φ(t), with θ(t) =

$\theta_{Midpoint} + \theta_{Amplitude}\ cos[\varphi(t) - \varphi_{Preferred}]$. (**b**) Plot of the touch response parsed according to the angular position of the vibrissa upon contact. The angle is relative to the midline of the animal's head. (**c**) Plot of the touch response parsed according to the phase in the whisk cycle upon contact; phase interval is $\pi/4$ radians. (**d**) Distribution of phase-shifts relative to the peak of protraction (panel a) for the set of units with both rapid and statistically significant responses to touch (28 out of 152 units in 9 rats) in addition to a phase preference for spiking while whisking in air. All panels adapted from reference 23.

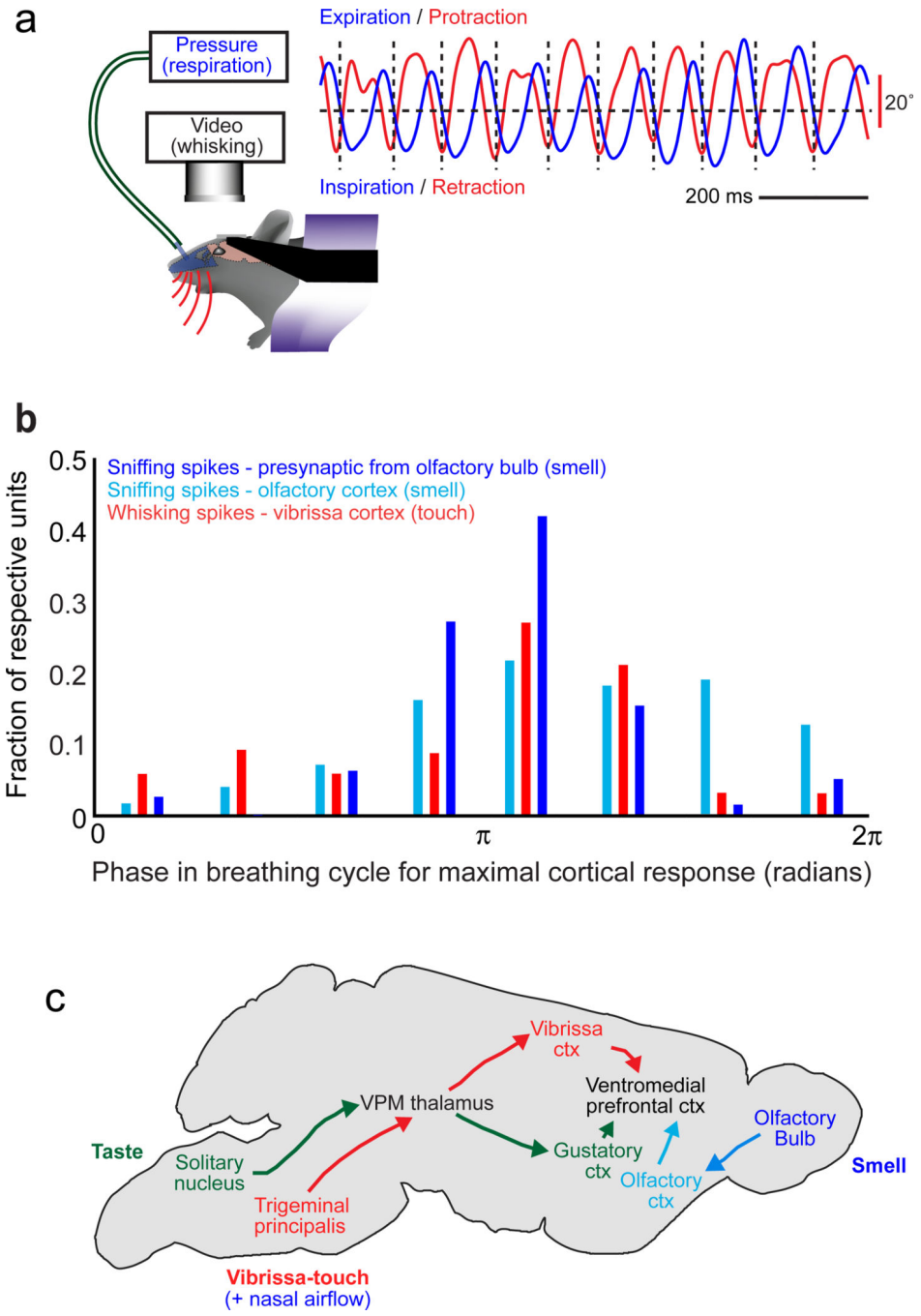

Figure 4. Coordination of sniffing and whisking and the potential functional and potential anatomical basis for binding of synchronous events

(a) Head-restrained mice, trimmed to a single vibrissa, were implanted with a pressure transducer in the nasal cavity and vibrissae were monitored with videography. The traces are simultaneous measurements of whisking and breathing. The dashed vertical lines highlight the simultaneous onset of protraction with that of inspiration. Adapted from reference 4. **(b)** Histograms of the preferred phases in the breathing cycle for smell for different units in the olfactory cortex (teal; Fig. 1d), smell for different units in the olfactory bulb (green; 312

responses from 87 units in 3 rats), and vibrissa-touch for different units in vibrissa cortex (red; Fig. 2). A phase shift to compensate for the time for output from the olfactory bulb to induce spikes in olfactory cortex, computed as (10 Hz)(0.018 s)(2 π) = 1.1 radians, where 10 Hz is a typical sniffing frequency for mice (7 Hz for rats) and 0.018 s is the delay, was used to shift the olfactory bulb responses (Fig. 2d). The olfactory data sets were binned to the resolution of the vibrissa data (Fig. 3d). **(c)** Schematic of convergent anatomical pathways of sensory input to the ventromedial prefrontal cortex. the abbreviation "VPM thalamus" refers to the dorsomedial aspect of the ventroposterior medial thalamic nucleus for vibrissa-touch and the parvocellular portion of the ventroposterior medial nucleus for gustatory input.