

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

David Kleinfeld^{1,2}, Martin Deschênes³, Fan Wang⁴ & Jeffrey D Moore¹

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. Here we evaluate the status of experimental evidence that pertains to this hypothesis.

The cycle-by-cycle control of breathing originates in the preBötzing complex, a cluster of neurons whose rhythmic output initiates every breath (reviewed in refs. 1,2) and thereby provides the motor drive to sample odors (Fig. 1a,b). Axons from the preBötzing 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 whisking⁴ and licking^{5,6}; the case for chewing is equivocal⁷. 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 airway⁸ (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 Adrian¹¹ over 70 years ago. More contemporary work with rats by Cury and Uchida showed that this relationship holds for all behaviorally relevant frequencies of breathing¹², and Uchida and Mainen found that perception of odorants is tightly coupled to the breathing cycle¹³. As a means to determine whether rodents code olfactory signals relative to a peripheral refferent signal, that is, a reference signal that is derived from sensation of the airflow, as opposed to an efferent copy of

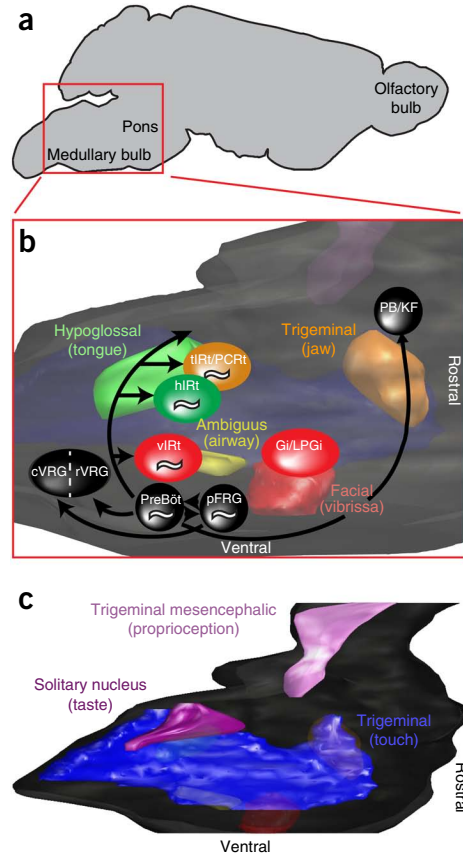
the respiratory drive, Sobel and Tank¹⁴ tracheotomized animals so that they breathed at their basal rate while the nasal airflow was modulated at an incommensurate frequency. These authors observed that neurons in the olfactory bulb indeed spiked in phase with the modulation in nasal airflow. This implies that a refferent signal, as opposed to an efference copy of breathing, is used as a reference signal. There are two likely origins of the peripheral refferent signal. First, Wallois and colleagues¹⁵ showed that primary trigeminal neurons that innervate the nasal cavity are activated in phase with breathing. Second, Ma and colleagues¹⁶ found 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 refferent signal to the olfactory cortex, but not to the olfactory bulb, for which the olfactory receptors appear to supply their own refferent signal. In summary, although breathing provides the active drive for olfaction, the motor reference for coding olfactory signals is derived through peripheral refference 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 was provided in a recent study by Shusterman, Smear, Koulakov and Rinberg¹⁷. 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 animals (Fig. 2a). As expected from past work, the spiking patterns of neurons in the olfactory bulb varied from odor presentation to presentation (Fig. 2b). However, when the spiking responses were aligned to the onset of the subsequent inspiration, and the time-base was warped to an average breath cycle, they were 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 glomeruli¹⁸, yet is surprising given the rapid kinetics of agonist binding to olfactory receptor neurons¹⁹. Although it is unclear from this study whether the observed phase differences are invariant to changes in respiratory tidal volume or odorant concentration¹⁹, or the frequency of sniffing²⁰, additional work from Rinberg and colleagues²¹ addressed the behavioral relevance of the timing of mitral cell activation in the breath cycle. They 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 in 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.

¹Department of Physics, University of California, San Diego, La Jolla, California, USA. ²Section of Neurobiology, University of California, San Diego, La Jolla, California, USA. ³Department of Psychiatry and Neuroscience, Centre de Recherche Université Laval Robert-Giffard, Québec City, Québec, Canada. ⁴Department of Neurobiology, Duke University Medical Center, Durham, North Carolina, USA. Correspondence should be addressed to D.K. (dk@physics.ucsd.edu).

Received 5 January; accepted 11 March; published online 25 April 2014;
doi:10.1038/nn.3693

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 pole and the locus of touch, texture and taste orofacial input through the pons and medullary bulb. The motor areas for all of these active senses are located in the medulla and pons. (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, whereas 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 refs. 1,3–5,48–50. Parvocellular reticular formation, PCRt; caudal and rostral ventral respiratory groups, cVRG and rVRG; trigeminal, hypoglossal and vibrissa intermediate reticular formation, tIRt, hIRt and vIRt; preBötzinger complex, Pre-BötC; parafacial respiratory group, pFRG; gigantocellular reticular formation, Gi; lateral paragigantocellular reticular formation, LPGi; parabrachial, PB; Kölliker-Fuse, KF. (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 (light purple) and gustatory inputs from the tongue innervate the solitary nucleus (dark purple).



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 Uchida²². The spike rates of neurons in this area were 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 whisking²³, with the strongest responses in layers 4 and 5a (refs. 23,24). Furthermore, 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 the animals actively explore the space around their head before contact with an object (summarized in ref. 28). Specifically, about half of the units throughout the depth of cortex have a spike rate that is significantly modulated by whisking²³. 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 whisk cycle and discarding the amplitude and midpoint of the whisk²⁸, was found to be derived from peripheral reafference^{31,32}. Furthermore, the spike rate of different units peak at different phases²⁸. Thus, spiking as a function of position in the whisk cycle provides a reference signal that is 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 sensing²³ (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. An analysis of the spike rate for units in primary vibrissa sensory cortex following contact as a function of angle in the whisk cycle shows an absence of tuning (Fig. 3b), that is, absolute position does not affect spiking. In contrast, an analysis of the spike rate for the same units 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 Welker³³ over 50 years ago. However, 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 breathing⁴. 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} (Fig. 4a). By combining the phase-dependent responses in sensory cortex during sniffing and whisking, we estimate

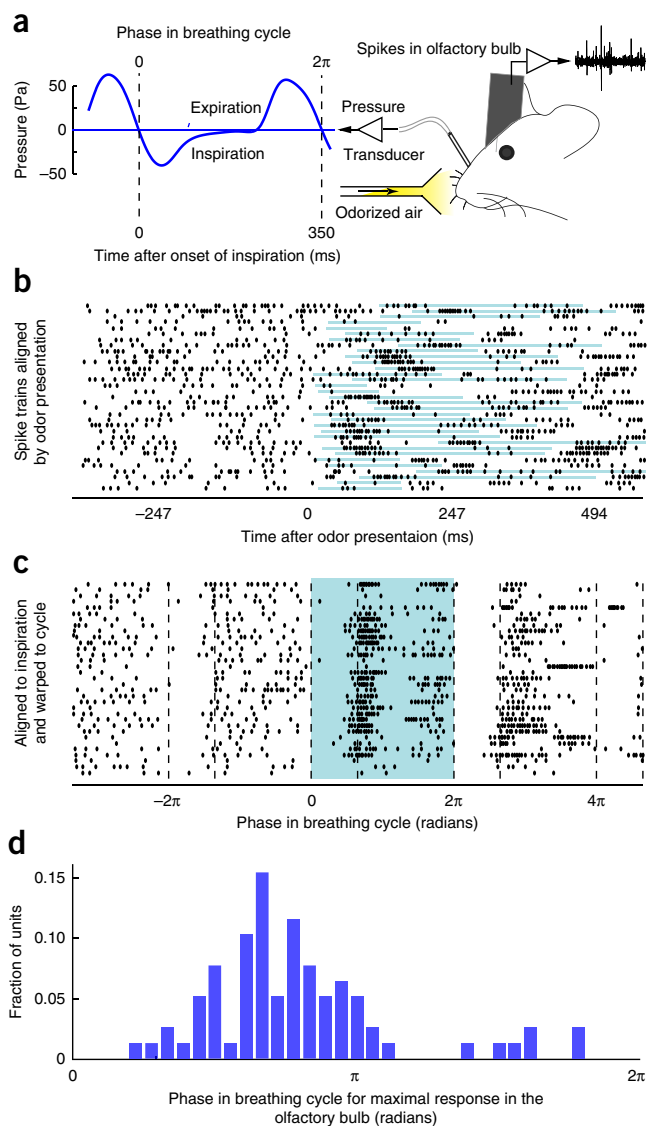


Figure 2 Smell is coded by projection neurons in the olfactory bulb whose spike rate is phase-locked to the breathing cycle. **(a)** An odor delivery port was positioned in front of the nose of a head-fixed mouse. The animal was implanted with an intranasal cannula to log pressure and infer breathing 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 **b**, but aligned by inspiration onset and temporally warped. The light blue shading indicates 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 phase-shifts of the neuronal responses relative to the onset of inspiration **(a)** for a set of high signal-to-noise responses (78 of 467 responses across 66 units in 7 mice). All panels are adapted from ref. 17.

that a substantial fraction of units in the olfactory cortex²² that respond to odors may spike in synchrony with units in vibrissa cortex that report touch²³ (Fig. 4b). A similar conclusion is reached when we express the phase response for units in the olfactory bulb in terms of their expected presynaptic activity at the olfactory cortex¹⁷; that is, correcting for the propagation and synaptic delays from the olfactory bulb to cortex³⁵ (Fig. 4b). We emphasize that these comparisons are

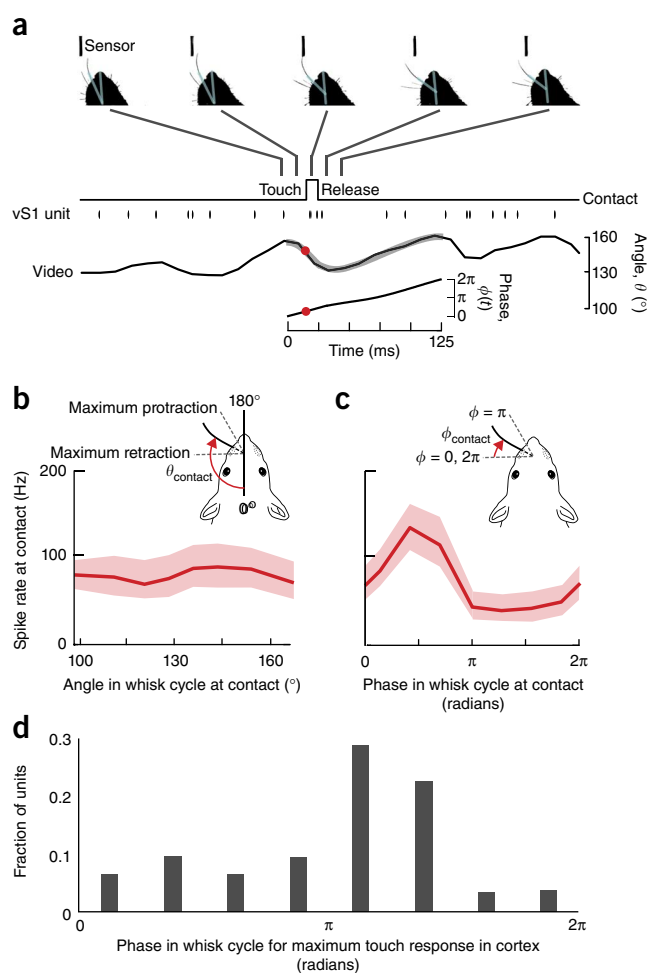
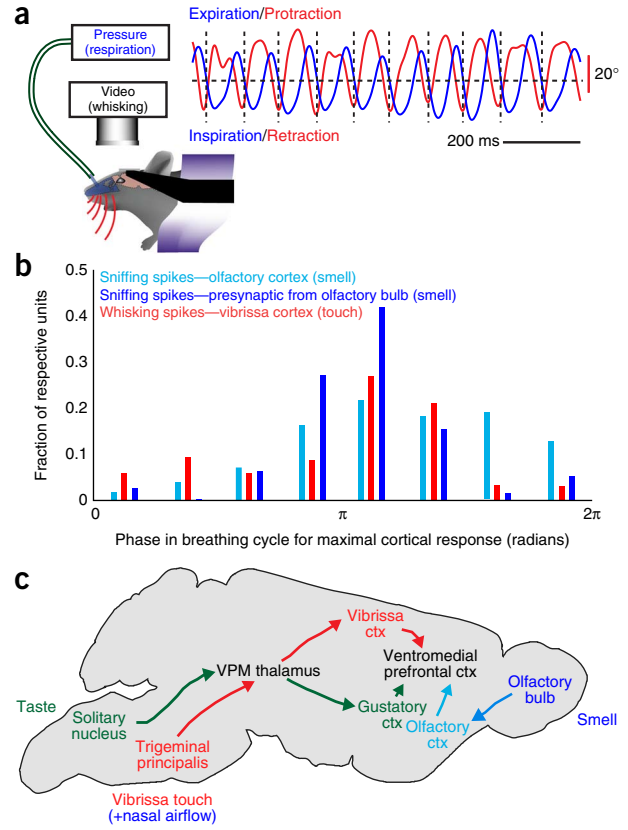


Figure 3 Vibrissa touch during exploratory whisking is coded by neurons in layer 4 and 5a of primary vibrissa cortex. **(a)** The rat, trimmed to single vibrissa, is held in a sock that lines a plastic tube, cranes from a perch to contact a piezoelectric touch sensor. Spike signals from multiwire-electrodes 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 unit. The angle, $\theta(t)$, for the cycle with a contact event is decomposed into phase, $\phi(t)$, with $\theta(t) = \theta_{\text{Midpoint}} + \theta_{\text{Amplitude}} \cos[\phi(t) - \phi_{\text{Preferred}}]$. **(b)** Plot of the touch response parsed according to the angular position of the vibrissa following contact. The angle is relative to the midline of the animal's head. The shaded region is the 95% confidence interval. **(c)** Plot of the touch response parsed according to the phase in the whisk cycle upon contact for the same unit as in **b**. The shaded region is the 95% confidence interval. **(d)** Distribution of phase shifts relative to the peak of protraction **(a)** for the set of units with both rapid and statistically significant responses to touch (28 of 152 units in 9 rats) in addition to a phase preference for spiking while whisking in air. All panels adapted from ref. 23.

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

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 ref. 4. **(b)** Histograms of the preferred phases in the breathing cycle for smell for different units in the olfactory cortex (light blue; **Fig. 2d**), smell for different units in the olfactory bulb (dark blue; 312 responses from 87 units in 3 rats) and vibrissa touch for different units in vibrissa cortex (red; **Fig. 3d**). A phase shift to compensate for the time for output from the olfactory bulb to induce spikes in olfactory cortex, computed as $(10 \text{ Hz})(0.018 \text{ s})(2\pi) = 1.1$ 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. 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.



to an object with a particular smell at a particular location relative to the face. Furthermore, the observed phase-locking between sniffing and head-bobbing³³ 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 licking⁵ 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 (**Fig. 1b**).

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, furthermore, can function as detectors of phase-locked, but not synchronous, depolarizing inputs with the use of active dendritic processes³⁶. The situation for neurons with mixed excitatory and inhibitory inputs, which is particularly relevant for cortical neurons³⁷, 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 in spiking rate³⁸. Thus, the overlap of the phase response curves for sniffing and whisking (**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 alone³⁹. 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 cycle²¹. 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 with 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 aggregate spike count in primary sensory cortex³⁹. 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 targets²⁶. 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, this high-level region receives direct projections from olfactory, gustatory and somatosensory cortical areas⁴⁰ (**Fig. 4c**). A second likely candidate for multimodal integration, first noted by Johnston⁴¹ 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 cortex⁴². 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 amygdala⁴³. The results of a lesion study in the medical literature highlight medial dorsal nucleus as a functional locus for the integration of orofacial stimuli⁴⁴. These anatomical substrates provide targets for an

© 2014 Nature America, Inc. All rights reserved. npg

experimental program on neuronal recording during a multimodal behavior task. One ethologically relevant 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 has a prominent role in the formation of new memories in the hippocampus and the amygdala. Furthermore, 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 behaviors⁴⁵, one cannot exclude the possibility that sniffing, whisking, head-bobbing and possibly tasting may transiently synchronize the θ -rhythm with respiration⁴⁶, particularly in the presence of stimuli of intense behavioral interest⁴⁷. We suggest that such synchrony would facilitate the formation of memories that involve a confluence of orofacial senses.

ACKNOWLEDGMENTS

This Perspective is dedicated to the late John C. Curtis. We thank W. Denk, B. Friedman, J.S. Isaacson, S. Jacobson, H.J. Karten, T. Komiyama, D. Rinberg and K. Svoboda for discussions, and K. Miura, D. Rinberg and N. Uchida for supplying data sets. This perspective was conceived at a 2013 Janelia Farms Research Center meeting and the subsequent work was supported by grants from the National Institute of Mental Health (MH085499), the National Institute of Neurological Disorders and Stroke (NS058668 and NS077986), the Canadian Institutes of Health Research (grant MT-5877), and the US-Israeli Binational Foundation (2011432).

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Reprints and permissions information is available online at <http://www.nature.com/reprints/index.html>.

- Feldman, J.L. & Del Negro, C.A. Looking for inspiration: new perspectives on respiratory rhythm. *Nat. Rev. Neurosci.* **7**, 232–242 (2006).
- Garcia, A.J., Zanella, S., Koch, H., Doi, A. & Ramirez, J.M. Networks within networks: the neuronal control of breathing. *Prog. Brain Res.* **188**, 31–50 (2011).
- Tan, W., Pagliardini, S., Yang, P., Janczewski, W.A. & Feldman, J.L. Projections of preBötzing complex neurons in adult rats. *J. Comp. Neurol.* **518**, 1862–1878 (2010).
- Moore, J.D. *et al.* Hierarchy of orofacial rhythms revealed through whisking and breathing. *Nature* **497**, 205–210 (2013).
- Travers, J.B., Dinardo, L.A. & Karimnamazi, H. Motor and premotor mechanisms of licking. *Neurosci. Biobehav. Rev.* **21**, 631–647 (1997).
- Koizumi, H. *et al.* Functional imaging, spatial reconstruction, and biophysical analysis of a respiratory motor circuit isolated *in vitro*. *J. Neurosci.* **28**, 2353–2365 (2008).
- McFarland, D.H. & Lund, J.P. An investigation of the coupling between respiration, mastication, and swallowing in the awake rabbit. *J. Neurophysiol.* **69**, 95–108 (1993).
- Sherrey, J.H. & Megirian, D. State dependence of upper airway respiratory motoneurons: functions of the cricothyroid and nasolabial muscles of the unanesthetized rat. *Electroencephalogr. Clin. Neurophysiol.* **43**, 218–228 (1977).
- Singer, W. & Gray, C.M. Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* **18**, 555–586 (1995).
- Varela, F., Lachaux, J.-P., Rodriguez, E. & Martinerie, J. The brainweb: phase synchronization and large-scale integration. *Nat. Rev. Neurosci.* **2**, 229–239 (2001).
- Adrian, E.D. Olfactory reactions in the brain of the hedgehog. *J. Physiol. (Lond.)* **100**, 459–473 (1942).
- Cury, K.M. & Uchida, N. Robust odor coding via inhalation-coupled transient activity in the mammalian olfactory bulb. *Neuron* **68**, 570–585 (2010).
- Uchida, N. & Mainen, Z.F. Speed and accuracy of olfactory discrimination in the rat. *Nat. Neurosci.* **6**, 1224–1229 (2003).
- Sobel, E.C. & Tank, D.W. Timing of odor stimulation does not alter patterning of olfactory bulb unit activity in freely breathing rats. *J. Neurophysiol.* **69**, 1331–1337 (1993).
- Wallois, F., Macron, J.M., Jounieaux, V. & Duron, B. Trigeminal nasal receptors related to respiration and to various stimuli in rats. *Respir. Physiol.* **85**, 111–125 (1991).
- Grosman, X., Santarelli, L.C., Tan, J., Luo, M. & Ma, M. Dual functions of mammalian olfactory sensory neurons as odor detectors and mechanical sensors. *Nat. Neurosci.* **10**, 348–354 (2007).
- Shusterman, R., Smear, M.C., Koulakov, A.A. & Rinberg, D. Precise olfactory responses tile the sniff cycle. *Nat. Neurosci.* **14**, 1039–1044 (2011).
- Dhawale, A.K., Hagiwara, A., Bhalla, U.S., Murthy, V.N. & Albeanu, D.F. Non-redundant odor coding by sister mitral cells revealed by light addressable glomeruli in the mouse. *Nat. Neurosci.* **13**, 1404–1412 (2010).
- Reisert, J. & Zhao, H. Response kinetics of olfactory receptor neurons and the implications in olfactory coding. *J. Gen. Physiol.* **138**, 303–310 (2011).
- Carey, R.M. & Wachowiak, M. Effect of sniffing on the temporal structure of mitral/tufted cell output from the olfactory bulb. *J. Neurosci.* **31**, 10615–10626 (2011).
- Smear, M., Shusterman, R., O'Connor, R., Bozza, T. & Rinberg, D. Perception of sniff phase in mouse olfaction. *Nature* **479**, 397–400 (2011).
- Miura, K., Mainen, Z.F. & Uchida, N. Odor representation in olfactory cortex: distributed rate coding and decorrelated population activity. *Neuron* **74**, 1087–1098 (2012).
- Curtis, J.C. & Kleinfeld, D. Phase-to-rate transformations encode touch in cortical neurons of a scanning sensorimotor system. *Nat. Neurosci.* **12**, 492–501 (2009).
- O'Connor, D.H., Peron, S.P., Huber, D. & Svoboda, K. Neural activity in barrel cortex underlying vibrissa-based object localization in mice. *Neuron* **67**, 1048–1061 (2010).
- O'Connor, D.H. *et al.* Vibrissa-based object localization in head-fixed mice. *J. Neurosci.* **30**, 1947–1967 (2010).
- Mehta, S.B., Whitmer, D., Figueroa, R., Williams, B.A. & Kleinfeld, D. Active spatial perception in the vibrissa scanning sensorimotor system. *PLoS Biol.* **5**, e15 (2007).
- Knutsen, P.M., Pietr, M. & Ahissar, E. Haptic object localization in the vibrissal system: behavior and performance. *J. Neurosci.* **26**, 8451–8464 (2006).
- Kleinfeld, D. & Deschênes, M. Neuronal basis for object location in the vibrissa scanning sensorimotor system. *Neuron* **72**, 455–468 (2011).
- Szwed, M., Bagdasarian, K. & Ahissar, E. Coding of vibrissal active touch. *Neuron* **40**, 621–630 (2003).
- Hires, S.A., Pammer, L., Svoboda, K. & Golomb, D. Tapered whiskers are required for active tactile sensation. *Elife* **2**, e01350 (2013).
- Fee, M.S., Mitra, P.P. & Kleinfeld, D. Central versus peripheral determinates of patterned spike activity in rat vibrissa cortex during whisking. *J. Neurophysiol.* **78**, 1144–1149 (1997).
- Poulet, J.F. & Petersen, C.C. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. *Nature* **454**, 881–885 (2008).
- Welker, W.I. Analysis of sniffing of the albino rat. *Behav.* **22**, 223–244 (1964).
- Ranade, S., Hangya, B. & Kepecs, A. Multiple modes of phase locking between sniffing and whisking during active exploration. *J. Neurosci.* **33**, 8250–8256 (2013).
- Ketchum, K.L. & Haberly, L.B. Membrane currents evoked by afferent fiber stimulation in rat piriform cortex. I. Current source-density analysis. *J. Neurophysiol.* **69**, 248–260 (1993).
- Vaidya, S.P. & Johnston, D. Temporal synchrony and gamma-to-theta power conversion in the dendrites of CA1 pyramidal neurons. *Nat. Neurosci.* **16**, 1812–1820 (2013).
- Haider, B., Duque, A., Hasenstaub, A.R. & McCormick, D.A. Neocortical network activity *in vivo* is generated through a dynamic balance of excitation and inhibition. *J. Neurosci.* **26**, 4535–4545 (2006).
- Salinas, E. & Sejnowski, T.J. Impact of correlated synaptic input on output firing rate and variability in simple neuronal models. *J. Neurosci.* **20**, 6193–6209 (2000).
- O'Connor, D.H. *et al.* Neural coding during active somatosensation revealed using illusory touch. *Nat. Neurosci.* **16**, 958–965 (2013).
- Rolls, E.T. The rules of formation of the olfactory representations found in the orbitofrontal cortex olfactory areas in primates. *Chem. Senses* **26**, 595–604 (2001).
- Johnston, J.B. Further contributions to the study of the evolution of the forebrain. *J. Comp. Neurol.* **35**, 337–481 (1923).
- McDonald, A.J. Cortical pathways to the mammalian amygdala. *Prog. Neurobiol.* **55**, 257–332 (1998).
- Ray, J.P. & Price, J.L. The organization of the thalamocortical connections of the mediodorsal thalamic nucleus in the rat, related to the ventral forebrain-prefrontal cortex topography. *J. Comp. Neurol.* **323**, 167–197 (1992).
- Rousseaux, M., Muller, P., Gahide, I., Mottin, Y. & Romon, M. Disorders of smell, taste, and food intake in a patient with a dorsomedial thalamic infarct. *Stroke* **27**, 2328–2330 (1996).
- Berg, R.W., Whitmer, D. & Kleinfeld, D. Exploratory whisking by rat is not phase-locked to the hippocampal theta rhythm. *J. Neurosci.* **26**, 6518–6522 (2006).
- Margrie, T.W. & Schaefer, A.T. Theta oscillation coupled spike latencies yield computational vigour in a mammalian sensory system. *J. Physiol. (Lond.)* **546**, 363–374 (2003).
- Macrides, F., Eichenbaum, H.B. & Forbes, W.B. Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. *J. Neurosci.* **2**, 1705–1717 (1982).
- Nakamura, Y. & Katakura, N. Generation of masticatory rhythm in the brainstem. *Neurosci. Res.* **23**, 1–19 (1995).
- Takato, J. *et al.* New modules are added to vibrissal premotor circuitry with the emergence of exploratory whisking. *Neuron* **77**, 346–360 (2013).
- Travers, J.B., Herman, K. & Travers, S.P. Suppression of 3rd ventricular NPY-elicited feeding following medullary reticular formation infusion of muscimol. *Behav. Neurosci.* **124**, 225–233 (2010).