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The Sniff as a Unit of Olfactory Processing

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Abstract

Sniffing is a rhythmic motor process essential for the acquisition of olfactory information. Recent behavioral experiments show that using a single sniff rats can accurately discriminate between very similar odors and fail to improve their accuracy by taking multiple sniffs. This implies that each sniff has the potential to provide a complete snapshot of the local olfactory environment. The discrete and intermittent nature of sniffing has implications beyond the physical process of odor capture as it strongly shapes the flow of information into the olfactory system. We review electrophysiological studies—primarily from anesthetized rodents—demonstrating that olfactory neural responses are coupled to respiration. Hence, the "sniff cycle" might play a role in odor coding, by allowing the timing of spikes with respect to the phase of the respiration cycle to encode information about odor identity or concentration. We also discuss behavioral and physiological results indicating that sniffing can be dynamically coordinated with other rhythmic behaviors, such as whisking, as well as with rhythmic neural activity, such as hippocampal theta oscillations. Thus, the sniff cycle might also facilitate the coordination of the olfactory system with other brain areas. These converging lines of empirical data support the notion that each sniff is a unit of olfactory processing relevant for both neural coding and inter-areal coordination. Further electrophysiological recordings in behaving animals will be necessary to assess these proposals.

Key words: active sensation, gamma rhythm, hippocampus, neural coding, theta rhythm, whisking

Introduction

Our sense of smell relies on sniffing to explore the olfactory world. Sniffing is common to terrestrial vertebrates—it is the process of inhaling rhythmically through the nose. Indeed, sniffing is an active form of sensory sampling adapted to the demands of olfaction; it creates the advection, or bulk airflow, that is required to rapidly deliver odor molecules from the environment to olfactory receptors. Interestingly, many species in the animal kingdom—even those without a nose—use some form of "sniffing" for olfaction: from antennal flicking in crustaceans (Atema, 1995; Mellon, 1997) to jaw protrusions or "coughing" in fish (Nevitt, 1991).

As a consequence of sniffing, the world of odors is conveyed to us in discrete samples, olfactory "snapshots." Therefore, above and beyond its role in the physical process of capturing odorants, sniffing has significant implications for olfactory processing. The cycle of inhalation and exhalation regulates the timing of information flow into the olfactory system. Consequently, patterns of olfactory neural activity are constrained by a specific temporal frame that may limit some aspects of olfactory processing while enhancing others.

In this review we explore the idea that the sniff serves as a fundamental unit for processing the olfactory world. We will focus primarily on sniffing in rodents, where both behavioral and neurophysiological studies are available. We begin by considering behavioral and psychophysical data and then move to consider neural recordings in the olfactory system. Finally, we examine the relationship between sniffing and other rhythmic sensory, cognitive, and motor processes and explore the broader implications of the "sniff cycle" for the nervous system.

Behavioral studies on sniffing

Rats sniff, rhythmically drawing air through their noses, in order to transport volatile chemicals to receptors in the nasal epithelium. Thus, sniffing may be operationally defined as a series of rapid rhythmic nasal inhalations performed for the purpose of obtaining odor information from the environment. Because rats are obligate nose breathers, sniffing is distinguished from other nasal breathing patterns primarily by the rate of repetition. It is not entirely clear what parameters

of respiration are most relevant for olfaction, but it appears that flow rate increases with breathing frequency (Walker *et al.*, 1997) and in fact several measures of a ''sniff'' are correlated with each other (Youngentob *et al.*, 1987), suggesting that frequency by itself is informative. However, since even basal respiration frequencies are sufficient for smelling, it is difficult to quantitatively define the precise frequency or pattern of respiration that can be considered as sniffing (but see below). Partly owing to this definitional ambiguity and also because much of the available electrophysiological data are from anesthetized animals, we will use ''respiration'' and ''sniffing'' interchangeably unless specifically noted.

Under natural conditions, sniffing in rats is usually one aspect of a stereotyped exploratory behavioral pattern. Mildly novel visual, auditory, tactile, or olfactory cues can all induce such exploratory behavior. This was first characterized in detail in a classic study by Welker (1964) using video recordings. He described a relatively stereotyped movement sequence starting with head fixation, the protraction of vibrissae, a brief inhalation, and retraction of the tip of the nose. This phase is followed by vibrissae retraction, exhalation, and protraction of the nose; after a slight repositioning of the head, the sequence begins again (Figure 1). This entire cycle of movements repeats at around 4–12 Hz and tends to occur in bouts lasting 1–10 s (Youngentob *et al.*, 1987).

In rodents, sniffing has been observed to synchronize not only with whisking and head bobbing but also with the heartbeat and perhaps with other rhythmic movements such as chewing and licking (Komisaruk, 1970). All these behaviors occur at 4–12 Hz, a range of frequencies known as the ''theta'' (θ) band. Both the sniffing rhythm and the movement initiation can also be coupled to specific phases of the hippocampal theta rhythm (Semba and Komisaruk, 1978; Macrides *et al.*, 1982), a topic to which we will return. Although, in general, the function of such synchronization remains to be elucidated, next we discuss a clear example in which the behavioral significance of sniffing-coordinated movements is understood.

Active shaping of airflow during sniffing

Beyond the bulk airflow into the nose regulated by sniffing, in many mammals there is an accompanying movement of the nostrils. These nostril movements appear to control the aerodynamics of odorant flow around the external nares that lead to the nasal passages. Externally, the nostrils can provide directionality to inspired air (Negus, 1958) while the alar folds inside the nostril can further control the airflow into or out of the nasal cavity (Stoddart, 1980). To study the aerodynamics of flow outside the nose, airflow visualization methods have been used. In particular, Settles and colleagues have used the Schlieren method, an optical process that makes visible the changes in the index of refraction of air and therefore offers a sensitive assay for capturing changes in air temperature (Settles, 2005). These authors observed in dogs that the movement of the alar fold during inspiration allows air to flow in from the front, while during expiration this channel closes and the nostrils flare to direct airflow outward laterally (Settles *et al.*, 2003). Similarly, in rabbits and rats the nostril motion is driven by narial muscles coordinated with sniffing, and expired air is ejected in a ventrolateral direction (Glebovskii and Marevskaia, 1968; Bojsen-Moller and Fahrenkrug, 1971; Wilson and Sullivan, 1999).

Due to this active positioning, nostrils act as variable-geometry flow diverters inspiring air directly from the front of the animal and expiring it toward the back (Figure 2; Settles, 2005). As a result, odorants can be extracted from the environment while minimizing disturbance to the olfactory sample itself. This may be particularly important for precise odor tracking (Means *et al.*, 1971; Wallace *et al.*, 2002; Settles, 2005). Rhythmic sniffing and nostril movements will also entrain the surrounding air, creating a current

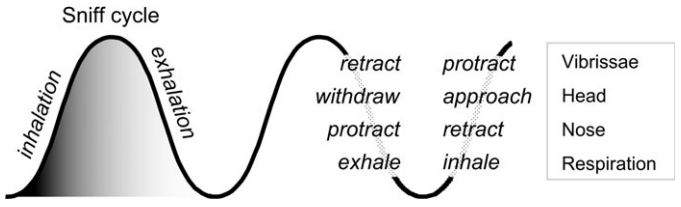

Figure 1 The sniff cycle. Sniffing is coordinated with several other motor rhythms on a cycle-by-cycle basis (after Welker, 1964).

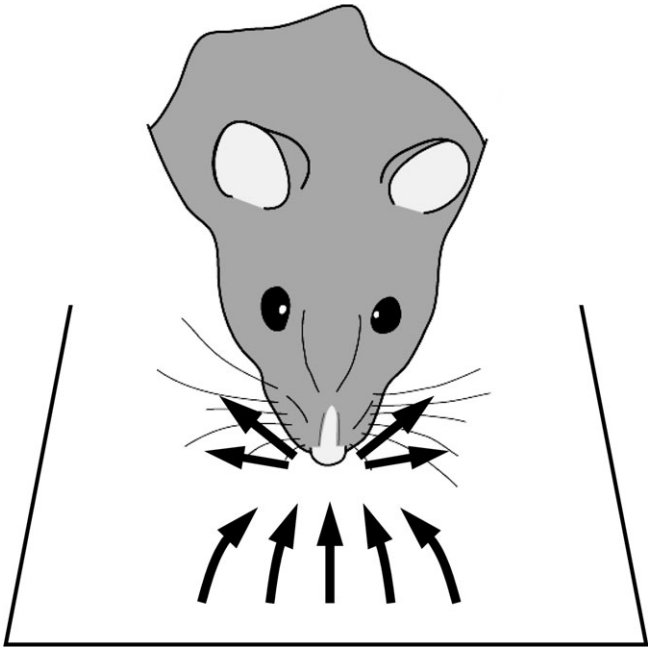

Figure 2 Aerodynamics of sniffing. A cartoon illustrating the airflow around the external nares due to the active control of the nostril during sniffing. Air is inspired omnidirectionally from the front and expired air is ejected in the ventrolateral direction (after Settles *et al.*, 2003). The coordination between sniffing and narial muscles creates favorable airflow dynamics to facilitate the acquisition of odor stimuli.

toward the nares, which can extend the "reach" of the nose (Settles *et al*., 2003). These observations demonstrate how the active control of sniffing and the accompanying aerodynamic optimization of airflow enhance olfactory sampling in animals. Ideas derived from these principles are starting to appear in artificial noses, a form of sniffing biomimicry (Settles and Kester, 2001).

Sniffing to discriminate

Animals often rely on olfactory cues to discriminate between friends and foes, danger and shelter, or fresh and rotten foods. Few studies have examined sniffing during such an olfactory discrimination process in its ethological context (Thesen *et al*., 1993; Steen *et al*., 1996). One notable study showed that dogs can reliably track footprints outdoors by sniffing at 6 Hz 10–20 times in a bout to find the track, then slow down to take 30–40 sniffs at 2–5 footprints to decide a track's direction (Thesen *et al*., 1993). While more work is needed to understand sniffing in its natural setting, insights into the role of sniffing have also come from studies with animals trained to smell and discriminate using operant or classical conditioning procedures.

One sniff is enough for accurate discrimination

In an early study on sniffing during olfactory discrimination, Karpov (1980) trained rabbits to explore a set of boxes in which an odor cue indicated the presence or absence of available food. He recorded the sniffing pattern as well as neuronal activity in the olfactory bulb and noted that in one respiration cycle (~250 ms) rabbits were able to complete an odor discrimination (Karpov, 1980). Similarly, maximal odor identification accuracy could be achieved with a single sniff in humans (Laing, 1986). When sniff duration was controlled by an auditory cue, a sniff of 0.42 s (short for a human) was sufficient to identify an odor (Laing, 1986). An even more rapid (<200 ms) control of sniff strength is evident in humans, whereby flow rate is decreased as odor concentration is increased, presumably to facilitate concentration-independent odor percepts (Johnson *et al*., 2003). Human studies have also reported that neither perceived intensity nor detection threshold is affected by the number of sniffs taken by human subjects (Laing, 1983, 1985).

These findings indicate that, contrary to conventional wisdom, olfactory processing may occur relatively quickly, possibly being limited only by the duration of the sniff cycle itself. Yet none of these studies addressed the question of whether olfactory discriminations could be executed as rapidly when the difficulty of the discrimination (i.e., the similarity of the odors) is increased. Indeed, one human psychophysical study using odor mixtures reported long and variable response times (Wise and Cain, 2000).

Our group studied the speed of olfactory discrimination and its relationship to sniffing in rats using a two-alternative odor discrimination task (Figure 3a) (Uchida and Mainen, 2003). In this task, rats are trained to initiate a trial by making a nose "poke" into a central port, triggering the delivery of one of a set of odors. The animal then withdraws from the odor port at a time of its choosing (up to 1 s) and moves to either the left or the right choice port where correct responses are rewarded with water. The time between odor onset and the withdrawal of the snout from the odor port is the odor-sampling duration, a measure of reaction time (Figure 3b).

Respiration patterns were measured using a thermocouple implanted in one nasal cavity (Figure 4). Across the entire behavioral session the frequency of nasal respiration was extremely variable, ranging from as low as 2 Hz to as high as 12 Hz. However, during odor sampling, respiration rates were much more stereotyped, centered tightly at around 8 Hz. Therefore, at least under these behavioral conditions, we can quantitatively define sniffing: an 8.5 ± 1.5 Hz respiration mode. Rats maintained a basal respiration rate of 2–4 Hz and switched to this high-frequency sniffing mode shortly before odor port entry and remained tightly locked to this frequency throughout odor sampling. The switch between different modes occurred very rapidly, almost always within a single respiration cycle (Kepecs *et al*., 2005).

In order to test the effect of discrimination difficulty on sniffing, we used binary odor mixtures in different

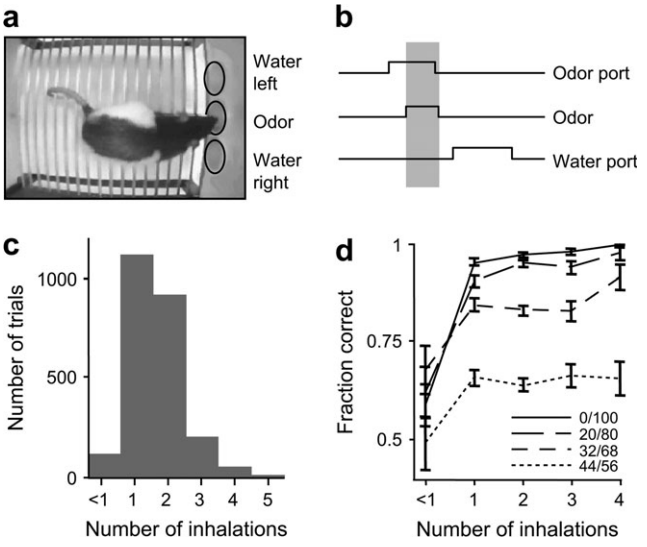

Figure 3 One sniff is enough for fine odor discrimination. **(a)** Still frame of a rat performing a two-alternative odor discrimination task. The rat is shown making a nose poke at the central odor port to trigger the delivery of an odor. Subsequently, the rat is rewarded for making a nose poke at the correct water port, depending on the identity of the odor. **(b)** Diagram of the timing of task events. Nose poke signals were recorded using photodetectors across the odor and water choice ports. The odor-sampling time is the latency from odor onset to withdrawal of nose from odor port (gray shading). **(c)** Distribution of the number of sniffs during the odor-sampling period for a single rat pooled across all trials (gray shading). The category "<1" contains trials with no inhalation or in which odor onset occurred during an inhalation. **(d)** Discrimination accuracy as a function of number of sniffs. Different lines correspond to different odor mixture ratios as indicated.

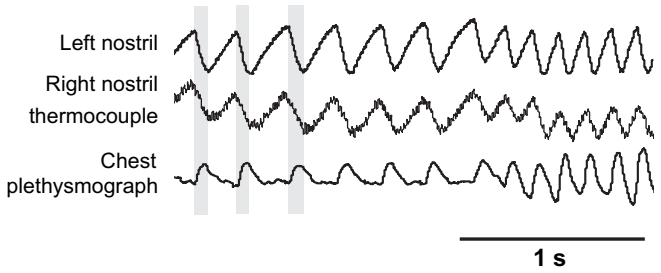

Figure 4 Measurement of sniffing. Concurrent recordings of two thermocouples in the left and right nostrils and a chest plethysmograph measuring respiration in a behaving rat. Two small thermocouples or temperature sensors were implanted into each nostril to detect the cooling and warming of air due to breathing (Angyan and Szirmai, 1967; Clarke *et al*., 1970). The thermocouples were inserted into the nasal passage through the nasal bone just rostral to the turbinates at about the same A–P positions and depth. The onset of inhalations and exhalations can be readily determined from the cooling–warming patterns. As a complementary method we also placed a piezoelectric respiratory belt around the rat's chest (Barrie *et al*., 1996). The device measures the expansion of the chest to indicate inhalations and exhalations. All signals were filtered between 0.1 and 50 Hz. Both thermocouples and the chest plethysmograph agree on a cycle-by-cycle basis with small (<30 ms) differences in time lags, although we have also observed that the thermocouple and the plethysmograph can transiently show dissimilar signals. Note the sudden respiration mode switch from 4 to 8 Hz and the accompanying change in the shape of the plethysmograph signal.

proportions (e.g., 100/0, 80/20, 68/32, 56/44, and 44/56) to produce discrimination problems with varying degrees of difficulty. In the mixture paradigm, different ratios were randomly interleaved in a session and responses were rewarded according to the dominant odor of the mixture. The use of interleaved mixtures produced a drop in performance for the most difficult mixtures (i.e., those closest to 50/50), but regardless of the difficulty, rats performed rapidly, taking just 200–300 ms odor-sampling time. Sniffing rate was approximately independent of odor parameters and nearly constant throughout the odor sampling period. Thus, at a rate of 8.5 Hz rats typically took one or two sniffs (median 1.96 ± 0.61) to discriminate odors (Figure 3c).

Is it possible that accuracy was higher for those trials during which the rat took several sniffs before responding? To address this issue, we examined how discrimination accuracy depended on the number of sniffs taken (Figure 3d). This "conditional accuracy" analysis takes advantage of the natural variability in the number of sniffs per trial within a single experimental condition. Trials were partitioned according to the number of sniffs and the discrimination accuracy was calculated for each condition. Trials with less than one full inhalation (odor onset occurring during the inhalation) resulted in poor performance, but performance reached an asymptote with a single sniff. There was a negligible (<5%) increase in accuracy for two sniff trials compared with one sniff trial and more sniffs failed to improve performance, regardless of the difficulty of the mixture discrimination (Figure 3d). Thus, accurate odor discrimination could be achieved with a single sniff (Uchida and Mainen, 2003). These results show that Karpov's (1980) observation that simple odor discrimination can be achieved with one sniff generalizes even to difficult discriminations.

The ability of rats (and, to some degree, humans) to perform rapid olfactory discrimination (Laing, 1986; Slotnick, 1990; Uchida and Mainen, 2003; Abraham *et al*., 2004) does not rule out the possibility that other olfactory tasks require additional processing time. Apparently, basic sensory discriminations are not a challenging task (in terms of time) for the well-trained brain. This appears to be true not only if the stimuli are very similar odors but even if they are complex visual scenes (Thorpe *et al*., 1996; Rousselet *et al*., 2002). Given the selective pressure for fast responses in most ecological settings, neural mechanisms that can achieve rapid processing of important stimulus characteristics may allow for more complex behaviors to be assembled in a timely fashion. Rapid sampling may also improve the fidelity with which olfactory "scenes" can be perceived. For example, as an animal moves around, the speed of odor processing relates directly to the precision with which that odor can be tagged to a specific spatial location. Similarly, the tracking of an odor source based on concentration gradients requires independent samples to be compared across time and would benefit from more rapid processing of individual samples.

Respiratory patterning of olfactory neural representations

A second major line of evidence supporting the idea that sniffing is critical for olfactory processing comes from electrophysiological findings showing that firing patterns of olfactory neurons depend strongly on the respiration cycle (Adrian, 1950; Walsh, 1956; Macrides and Chorover, 1972; Chaput and Holley, 1980; Pager, 1985; Chaput, 2000; Spors and Grinvald, 2002; Cang and Isaacson, 2003; Margrie and Schaefer, 2003; also see the chapter by Buonviso in this volume), a phenomenon known as respiratory patterning. Macrides and Chorover, who first analyzed the respiratory patterning of olfactory bulb mitral cells in anesthetized hamsters, noticed that different odor stimuli rarely resulted in large changes in firing rates but sometimes produced dramatic changes in the preferred respiration phase of responses (Figure 5c; Macrides and Chorover, 1972; Macrides, 1976).

Further investigation of respiratory patterning in awake animals was performed by Chaput and colleagues (Chaput and Holley, 1980; Chaput, 1986; Buonviso *et al*., 1992; Chaput *et al*., 1992). These authors first showed in awake rabbits that the responses of mitral and tufted (M/T) cells (the principle neurons of the olfactory bulb) became locked to the respiration cycle during odor stimulation (Chaput and Holley, 1980). Some olfactory bulb neurons increased their firing rate during inhalation and decreased their firing rate during exhalation, with little change in the overall rate across the sniff cycle (Figure 5a,b). Furthermore, the general

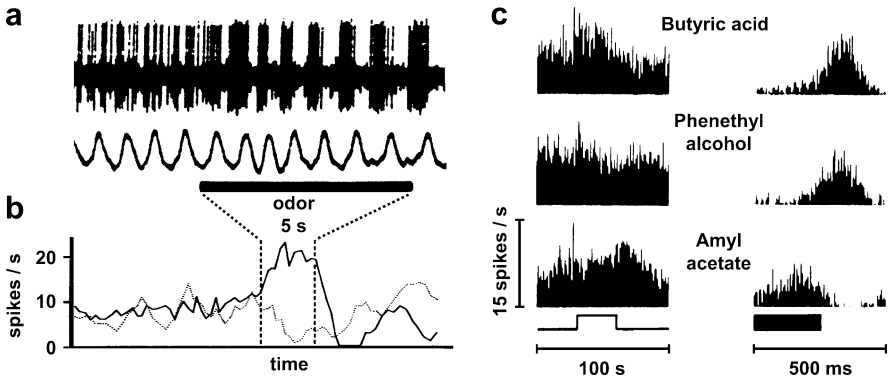

Figure 5 Respiratory patterning and phase encoding in the olfactory bulb. **(a)** Firing of an olfactory bulb neuron (top) and the respiration signal (below). During the 5 s of odor presentation, firing of this neuron locked to the respiration cycle (based on Figure 1a from Chaput and Holley, 1980). **(b)** Firing rate is separately plotted for the inhalation (solid line) and exhalation (dotted line) phases of respiration. The odor was presented between the dotted vertical lines (based on Figure 4b from Chaput and Holley, 1980). Data in (a) and (b) were obtained from an awake rabbit. **(c)** Firing rate changes in a gross timescale (left column) and firing rate changes within sniffing cycles (right column) are plotted for the same neuron. During the 30 s of odor stimulation, butyric acid (top), phenethyl alcohol (middle), and amyl acetate (bottom) were delivered. The respiratory cycle histogram is calculated for the odor presentation period. Data were recorded from an anesthetized hamster (Figure 2 from Macrides, 1976).

pattern of firing with respect to the respiration cycle changes little by varying the artificial breathing rate from 1 to 3 Hz (Macrides, 1976). It would be interesting to examine whether this remains true in awake animals during natural sniffing around the 8 Hz range. These findings demonstrate that knowing the respiration phase can provide additional information about odor responses beyond firing rate alone. We will return to the issue of how respiration phase might be important to neural information processing in the next section.

M/T cell responses are not limited to excitation during inhalation but can be both excitatory and inhibitory and show a variety of patterns with respect to the respiration cycle. Most M/T cells show a single peak of firing, which tends to occur between the end of inspiration and the beginning of the expiration phase (Buonviso *et al*., 1992). Different types of neurons in the olfactory bulb appear to be activated in a specific sequence within sniff cycles from early responses of cells in the glomerular layer, intermediate latencies from mitral cells, and late responses from granule cells in the deep layers (Buonviso *et al*., 2003). The mechanisms contributing to this sequencing are not well understood but presumably involve the dense inhibitory and excitatory feedback circuits formed between M/T cells and their (mainly) inhibitory partners, the juxtaglomerular neurons (glomerular layer) and granule cells (deep layers) (Hayar *et al*., 2004). Studies in the piriform cortex showed that olfactory neurons in this area also fire at specific phases of the respiration cycle (Bressler, 1987; Wilson, 1998; Buonviso *et al*., 2003). Therefore, the respiratory cycle sets the temporal window of activation for different neuron types across the olfactory system.

Additional information about the relationship between neural activity and the sniffing cycle comes from observations of population neuronal activity measured using local field potentials (LFPs). Strong oscillatory patterns are often observed in olfactory bulb LFPs (Adrian, 1942, 1950). As mentioned earlier, the sniffing rhythm corresponds to theta frequency, a band of oscillations commonly seen in olfactory LFPs. This relatively slow rhythm modulates the faster (20–100 Hz) rhythms that reflect the synchronization of populations of neurons in the olfactory bulb or olfactory cortex (Adrian, 1942; Bressler and Freeman, 1980). This higher frequency range is typically subdivided into the beta (β, 20–35 Hz) and gamma (γ, 35–100 Hz) bands. A classically described LFP pattern in the olfactory bulb consists of a few cycles of gamma oscillations riding on the theta waves (Barrie *et al*., 1996). Both beta and gamma oscillations show phase locking to the theta/sniffing rhythm, with beta and gamma oscillations waxing and waning in alternation (Buonviso *et al*., 2003). Although LFPs are an indirect measure of neuronal activity, it is important to note that M/T cells in the olfactory bulb can synchronize their spiking to LFPs even at these faster frequencies (Kashiwadani *et al*., 1999). Such fine-scale synchronization of neurons will increase their postsynaptic impact on downstream neurons.

An important caveat to the general rules relating neural activity in the olfactory system to the respiratory cycle is provided by the observation that brain state and behavioral context can strongly modulate the modes of oscillatory activity seen in the olfactory bulb and cortex of awake, and especially behaving, animals (Skarda and Freeman, 1987; Kay and Freeman, 1998). In particular, it has been reported that during active sniffing (i.e., at higher respiratory frequencies) M/T responses are more variable (Bhalla and Bower, 1997; Kay and Laurent, 1999) and may become uncoupled from the respiratory cycle (Kay and Laurent, 1999).

Coding within the sniff cycle

What is the functional significance of respiratory patterning of neural activity? A default hypothesis might be that

neuronal responses are simply reflections of the sensory input, which in the case of olfaction happens to arrive in intermittent pulses. In the following sections, we review a variety of indirect evidence supporting the idea that the sniffing cycle may have a significant functional role in neural coding and communication. To complement experimental evidence from olfaction, we will also draw some examples from the whisker system and the hippocampus where a richer body of work supports neuronal processing within the ''whisking cycle'' or ''theta cycle,'' respectively.

Time, phase, and neural codes

Whereas time is used in vision and other sensory systems to track the unfolding temporal dynamics of stimuli, the perception of odors does not appear to depend greatly on detecting temporal structure on timescales shorter than the sniff cycle itself. It is likely that an individual sniff abolishes any spatiotemporal inhomogeneities that might have been present in the olfactory environment, conveying essentially a bolus of odor molecules. Hence, the frequency of respiration represents an upper limit on the relevant timescale for the representation of stimulus temporal dynamics. Because the timescale of respiration is relatively slow from a neural perspective, there remains some extra ''temporal bandwidth'' to encode stimulus qualities rather than temporal changes in the stimulus. Consequently, the temporal pattern of spikes within each sniff cycle has the potential to represent some quality about the olfactory information, instead of encoding the dynamics of odor concentration in the environment.

As described earlier, olfactory neurons tend to phase lock their firing to specific phases of the respiration cycle. If these phase relationships were strictly fixed, then phase could not encode any additional information about the stimulus. However, variation in the phase relationships of individual M/T cells with the respiratory cycle could provide enough ''bandwidth'' to encode a stimulus parameter. What might that stimulus parameter be and how would phase encoding work?

Theta phase coding

A simple neural mechanism for phase encoding was proposed by Hopfield (1995). Consider the summation of a steady afferent input and an ongoing oscillatory respiratory drive. The stronger the afferent input, the earlier the cell will reach threshold during the oscillation cycle (Figure 6a). One straightforward expression of this phenomenon would be the encoding of concentration in latency, and experimental studies have provided evidence that varying odor concentration causes systematic changes in the spike latency or phase of spikes relative to the respiration cycle (Spors and Grinvald, 2002; Cang and Isaacson, 2003; Margrie and Schaefer, 2003). In particular, Cang and Isaacson (2003) showed that the amplitude and slope of odor-evoked excitatory postsynaptic potentials increase from low to high odor

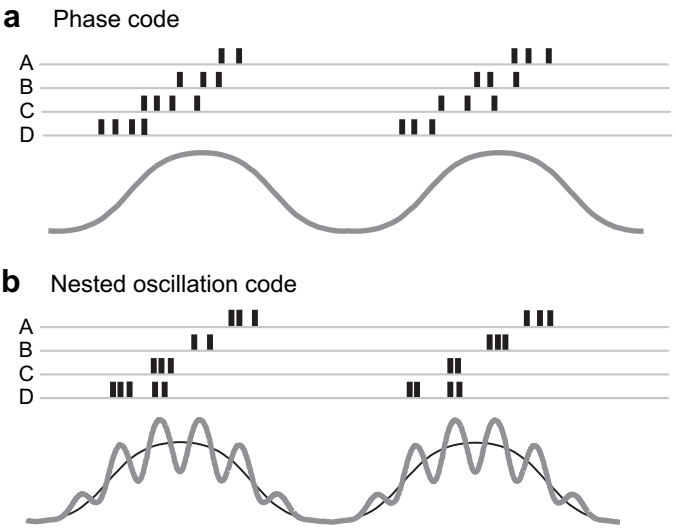

Figure 6 Odor coding within a sniff cycle. **(a)** Hypothesized activity of four neurons (A–D) using a "theta phase code." In principle, any kind of odor information could be encoded by the phase of spiking (black tick marks) with respect to the theta cycle (gray line). **(b)** Same as (a) for the "nested theta/gamma code." The ripples on the sniff cycle represent gamma subcycles, and neural activity is constrained to occur within these. The sequence of mitral cell activations across gamma subcycles is the basis of the code. Therefore, each group of coactivated mitral cells could be described as representing an "odor component," the sequence of which makes up an odor. Note, that this is only a neurophysiological definition of an odor component and without detailed modeling of the encoding process using nested oscillations, no direct prediction follows, although odor components might be relevant for understanding the problem of odor segmentation.

concentrations and a higher odor concentration generates earlier and longer bursts of action potentials coupled to the respiration cycle. In general, since response latency and firing rate were found to covary within a respiration cycle (Cang and Isaacson, 2003; Margrie and Schaefer, 2003), if concentration increases firing rate, then it will also be encoded in firing latency. However, it has also been observed that in some cases respiration-related patterns of activity can change dramatically (i.e., not simply with a latency change) with varying concentrations (Wellis *et al*., 1989).

Just as odor concentration can be encoded in firing latency, more generally, information about the degree of receptor activation can be encoded in the same way. Since the differential affinity of olfactory receptors to different odorants will create differential drive to glomeruli, odor identity can also, in principle, be encoded in respiratory phase as well as mitral cell firing rates (Hopfield, 1995, 1999). Indeed, Spors and Grinvald (2002) showed using voltage-sensitive dye imaging that different odors not only produced characteristic spatial patterns of glomerular activation but also produced distinct response latencies relative to respiration onset. A second process that might have contributed to these observations is the differential retention of various chemical species within the nasal epithelium, which could introduce odor-specific delays in glomerular activation, a kind of ''nasal chromatography''

(Mozell and Jagodowicz, 1973; Macrides, 1976; Spors and Grinvald, 2002). It should be noted that all these studies were performed in anesthetized animals at low respiration rates relative to active sniffing (~2 vs. ~8 Hz). Thus, although these theoretical and experimental studies have certainly opened the way, more studies of these phenomena are needed to understand under what conditions odor identity or concentration might be reliably encoded in respiratory phase in behaving animals.

While the existence of phase codes are still relatively speculative in the olfactory system, they are well established in its close cousin, the whisker system (Ahissar and Kleinfeld, 2003; Mehta and Kleinfeld, 2004). Whisking is the rhythmic protraction and retraction of facial vibrissae. Rats explore objects by whisking at frequencies in the theta range (5–15 Hz), and during exploration, the whisk cycle couples to sniffing (Welker, 1964). Many types of neurons across the whisker system—from the first relay at the trigeminal nucleus to the somatosensory cortex—fire at preferred phases of the whisk cycle. Trigeminal neurons respond both to the onset of a whisk cycle and at the time of object contact with the whisker, creating an interval code within a whisk cycle (Shipley, 1974; Ahissar *et al.*, 2000). In the primary somatosensory cortex, one class of neurons encodes the relative whisk phase of object contacts (Fee *et al.*, 1997). These neurons have "contact phase" tuning curves, with some cells firing more for early contacts and other cells firing more for late contacts. There is also accumulating evidence that reciprocal connections between the thalamus and the cortex (thalamocortical loops) can convert whisk-phase–coded spikes into a rate code (Ahissar *et al.*, 1997).

In the hippocampus, a structure involved in spatial navigation and memory, the theta cycle is also a fundamental unit of information processing. The hippocampus shows prominent theta-frequency oscillations during states of exploration and REM sleep (Buzsaki, 2002). In these states, cholinergic afferents and local interneurons entrain hippocampal pyramidal neurons to fire phase locked to the theta cycle (Dragoi *et al.*, 1999). Each pyramidal cell is activated at a particular place in the environment (hence, "place cells"). Not only is a cell's preferred "place" marked by an increase in firing rate but also by a systematic shift in the phase of spiking with respect to the theta rhythm (O'Keefe and Reece, 1993; Skaggs *et al.*, 1996). Indeed, the phase and instantaneous rate of spiking can be correlated (Harris *et al.*, 2002; Mehta *et al.*, 2002). This hippocampal population code allows the decoding of an animal's location based only on the firing rates of a small number of place cells (Wilson and McNaughton, 1993), and importantly, including phase information increases the precision with which the animal can be localized (Jensen and Lisman, 2000).

Thus, in both the whisker system and the hippocampus there is solid evidence for phase codes using the theta cycle, which is similar in frequency to the sniff cycle that patterns olfactory input. Moreover, analogies between olfactory and hippocampal processing have a strong anatomical basis. The hippocampus and olfactory system are both part of the limbic system and share direct and indirect reciprocal connections. In fact, a closer examination of hippocampal–olfactory population patterns suggests a variation on the basic theta phase code just discussed.

Nested oscillation coding

The hippocampus and olfactory system share not only the theta rhythm but also the prominence of faster gamma (35–100 Hz) ripples on top of each theta (4–12 Hz) cycle (Adrian, 1950; Vanderwolf, 1969; Bragin *et al.*, 1995; Barrie *et al.*, 1996). Based on the phenomenon of nested theta–gamma oscillations, Lisman proposed that a sequence of items held in memory may be represented by a sequence of neuronal ensembles firing in different gamma subcycles within a theta cycle (Lisman and Idiart, 1995). Thus, the theta cycle contains the entire "memory store" and each gamma cycle contains a single "item" in this memory. In the Lisman model, neural activity is constrained by inhibition to occur within a particular gamma subcycle (10–30 ms) (Figure 6b). The limited number of gamma cycles within the theta cycle was proposed to account for the limited capacity (famously 7 ± 2) of human working memory (Lisman and Idiart, 1995) and can also explain several observations about phase encoding by hippocampal place cells (Jensen and Lisman, 1996).

The nested oscillation model has been suggested to apply more broadly beyond the hippocampus (Lisman, 2005), for instance, for visual representations (VanRullen and Koch, 2003). Might nested oscillations be relevant for olfaction as well? This scheme might appear somewhat exotic, but a surprisingly generic network is capable of producing such neural representations. The nested oscillation code is produced by two components: inputs ramping at different rates that cause differential activation latencies and feedback inhibition from activated groups that shuts off the rest of the network for a short period, thus generating gamma cycles. For example, in the olfactory bulb, the differential affinities of receptors to different odors will generate glomerular activation rising at different rates. Feedback inhibition via juxtaglomerular and granule cells is thought to generate gamma oscillations. The neural code for odors using such nested oscillations will then be a sequence of mitral cell ensembles activated over successive gamma cycles (Figure 6b). Consistent with this, Spors and Grinvald (2002) observed sequential activation of glomeruli in an odor-specific manner at the timescale of few to tens of milliseconds (about a gamma cycle) and the temporal sequence was maintained across different odor concentrations. This code bears some resemblance to that observed in the locust antennal lobe, in which odors are represented by ensembles of neurons chunked by a beta-frequency oscillation (Wehr and Laurent, 1996). The chief difference is that the theta cycle sets

a limit on the number of steps (gamma cycles) in an odor representation.

There are overlapping as well as distinct predictions of a theta/gamma odor code compared to the pure theta phase code described earlier (Figure 6). Both neural codes predict that the phase of firing with respect to the sniff cycle encodes odor information. However, according to the theta/gamma model, the phase of firing within a sniff cycle will only be relevant up to the precision of a gamma subcycle (10–30 ms). Both coding schemes tend to preserve the rank order of responses, but the relative sequence of mitral cell activity across gamma subcycles is critical for the fidelity of a theta/gamma code.

Coordination using the sniff cycle

In the previous section we discussed the encoding of odor information within the olfactory system; now we consider the relationship between information in the olfactory system and that in other parts of the brain. Sniffing is synchronized to whisking and other rhythmic movements, as discussed earlier. What is the purpose of this synchronization? To obtain a clearer picture on this point, first we review evidence on how olfactory and other systems synchronize with each other at theta frequency. Next we briefly discuss previous theoretical ideas relevant for the topic before putting forward a proposal for the possible role of the sniff cycle in inter-areal coordination.

Theta-frequency synchronization is widespread in the brain. Neurons in the pons, locus coeruleus (Cohen and Wang, 1959), amygdala (Frysinger *et al.*, 1988), and other areas can lock their firing to the sniffing rhythm (i.e., theta-frequency oscillations). Meanwhile, the limbic or hippocampal theta rhythm has been shown to synchronize with a variety of other brain areas including prefrontal cortex (Borst *et al.*, 1987; Hyman *et al.*, 2005; Siapas *et al.*, 2005), mamillary nuclei (Kocsis and Vertes, 1994; Sharp, 2005), the amygdala (Seidenbecher *et al.*, 2003), the raphe nucleus (Kocsis and Vertes, 1992), and the inferior colliculus (Pedemonte *et al.*, 1996). The hippocampal theta rhythm can show selective phase relationships to the sniffing rhythm (Macrides *et al.*, 1982). Similarly, the olfactory bulb and the hippocampal theta rhythms can transiently synchronize (Kay, 2005).

One could imagine synchrony between areas arising simply out of anatomical constraints, but coherence of theta-frequency rhythms is not fixed but instead occurs transiently during specific behavioral states (e.g., Kocsis *et al.*, 1999; Ganguly and Kleinfeld, 2004). For example, olfactory bulb and hippocampal theta LFP oscillations can both be present without being coherent during a well-learned olfactory discrimination task (Kepecs and Mainen, 2004). Similarly, cortical theta-frequency oscillations are strongly gated by task demands in humans (Caplan *et al.*, 2003), and recording sites showing similar rhythms are not necessarily coherent (Raghavachari *et al.*, 2005), although the specific behavioral conditions for coherence are not understood. Insofar as coherence of disparate rhythms is confined to specific behavioral epochs (e.g., active exploration of a novel environment), it seems reasonable to take this coordination as a sign of an underlying process that serves a useful function in information processing. Further studies are required to understand the precise behavioral conditions eliciting synchrony across brain regions.

While in olfaction, rhythmic sampling almost requires the chunking of information, it seems surprising that other, largely nonsensory areas such as the amygdala or the hippocampus operate by discretizing information flow. A possible explanation is that sniffing at theta frequencies facilities flexible and specific coupling between olfactory and other neural systems by exploiting the sniff or theta cycle, a shared temporal frame across different brain areas.

Why chunk then link?

Why is coordination between brain areas even necessary? Because different sensory inputs (e.g., auditory vs. olfactory) and even stimulus ensembles (e.g., high vs. low contrast) are processed at different speeds by the nervous system (e.g., Albrecht *et al.*, 2002), the continuous processing of stimuli will create temporal ambiguities within the brain about the order of different sensory and motor events (Eagleman and Sejnowski, 2000; Schlag and Schlag-Rey, 2002). A simple solution may be to create discrete temporal frames or clock cycles to which neuronal activity may be referenced. A similar duration for the temporal frame in distinct brain areas would then enable easy coordination across different systems that process information at different timescales.

The notion of discrete temporal frames for perceptual processing date back several decades to psychophysical studies (Stroud, 1949) and related investigations of the visual alpha rhythm (Lindsley, 1952), neurophysiological work on cortical excitability cycles (Harter, 1967), and speculation about perception–action coupling. One important line of research showed that both visual reaction times (Lansing, 1957; Callaway and Yeager, 1960; Milstein, 1974) and even qualitative features of perception in humans (Varela *et al.*, 1981) depend on the phase of alpha oscillations (10–15 Hz) at which the stimulus arrives. Although, recent studies suggest that the perceptual impact of alpha phase may be subtle (VanRullen and Koch, 2003). Similarly, under some conditions, rats initiate movements at particular phases of the hippocampal theta cycle (Buno and Velluti, 1977; Semba and Komisaruk, 1978), although a recent study concluded that theta phase locking of movements was infrequent and inconsistent across subjects (Sinnamon, 2005). All these results hint at the potentially powerful effects of temporal chunking on sensorimotor coordination. Unfortunately, the present evidence is not sufficient to reveal the exact circumstances and

behavioral effects of temporal frames produced by neural oscillations.

Based on the preponderance of theta-frequency coupling between different behaviors and brain regions, Komisaruk (1977) proposed that the theta rhythm subserves sensory–motor integration. Specifically, he suggested that sensory and motor processing takes place sequentially at consecutive phases of each theta cycle. Despite the many years since this original proposal, there is still a lacuna in experiments addressing this issue, but there have been a few related theoretical proposals.

For example, Hasselmo *et al.* (2002) have suggested that the encoding and readout of memories occur at distinct phases of the hippocampal theta cycle. According to another idea, phase-encoded information can be differentially readout by phase shifting the decoder (Ahissar, 1998; Jensen, 2001), and experimental evidence supports this in the whisker thalamocortical system (Ahissar *et al.*, 1997).

The theta cycle as a communication protocol

How might the sniff cycle set the temporal frame for information transmission in the olfactory system? First, separate phases could correspond to feedforward versus feedback processing. Since different cell types in the olfactory bulb have different preferred response phases, their ease of activation by external inputs is likely to depend on phase. For instance, cell types that receive feedback from the olfactory cortex (i.e., granule cells) will be more excitable at particular phases of the sniff cycle and inhibited at other phases (Buonviso *et al.*, 2003), thus producing a temporal gate on the influence of feedback. The rest of the cycle would then favor feedforward processing. In this way, olfactory bulb computations might progress through an iteration of feedforward and feedback processing in each sniff cycle (Figure 7a).

A related idea is that specific kinds of information are present at distinct phases of the sniff cycle such that downstream brain areas could specialize in reading out certain types of odor information (Jensen, 2001). For instance, the earliest mitral cell responses might represent a coarse encoding of odor qualities, while at later phases lateral feedback could refine odor representations. In this scenario, the olfactory cortex, in order to form a detailed representation of an olfactory scene, might be interested in information at all phases, while the amygdala, in order to respond quickly to a significant odor, might respond to spikes early in the sniff cycle. This would be straightforward to implement neuronally, by amygdalar theta oscillations that are synchronized with the sniffing cycle but shifted in phase (Figure 7b). As a result, inputs from the olfactory bulb would only activate amygdalar neurons early in the bulb theta cycle, when amygdalar neurons are near activation threshold, which happens at the peak of the phase-shifted amygdalar theta rhythm. This example illustrates how phase-shifting–synchronized theta rhythms across brain areas could specifically gate information flow.

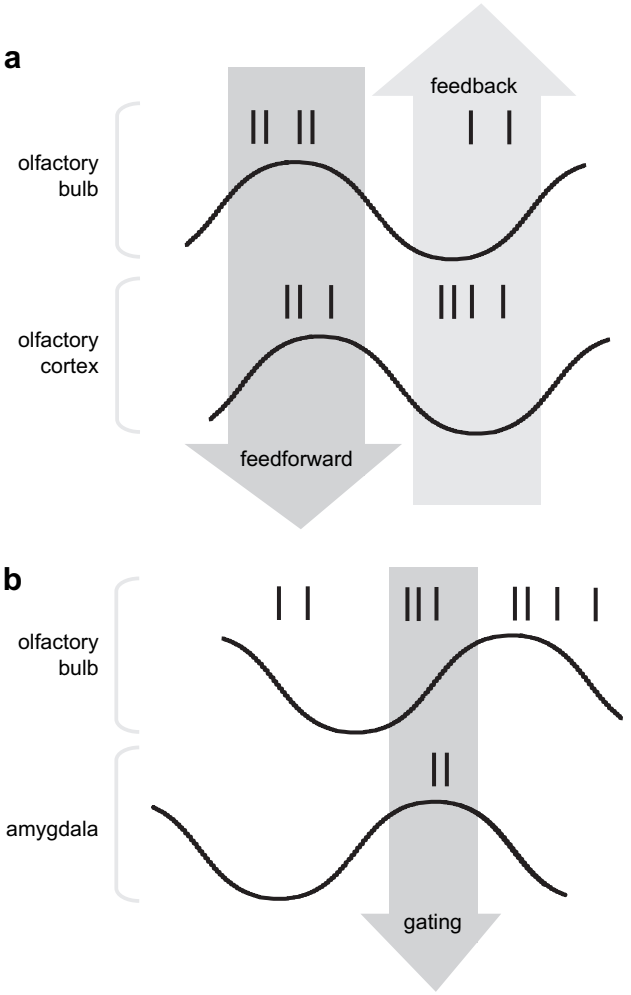

Figure 7 Theta cycle as a communication protocol. **(a)** Two areas with synchronized theta rhythms could use the theta cycle to disambiguate between feedforward-driven (e.g., sensory) and feedback-driven (e.g., expectation) representations. Therefore, olfactory bulb computations could progress through an iteration of feedforward and feedback processing in each sniff cycle. At different phases, distinct neurons or even classes of neurons could be active; thus, the spike trains represent a brain area and not a single neuron. **(b)** Two areas with coupled but phase-shifted theta rhythms could engage in selective gating of information. For instance, the amygdala, in order to react quickly to a significant event could selectively respond to spikes early in the sniff cycle, which might represent a coarse encoding of odor quality.

Conclusion

Sniffing, or discrete intermittent sampling, presents opportunities and constraints for olfactory processing. The sniffing rate limits the temporal resolution of incoming odor information, yet it also presents a temporal frame within which stimulus dynamics are fixed, thereby allowing the olfactory system to exploit this temporal frame as desired. We described several lines of evidence that this temporal

frame, the sniff cycle, is important beyond the sampling process.

Recent psychophysical behavioral experiments show that rats can perform fine odor discrimination with a single sniff (Figure 3; Uchida and Mainen, 2003). These results suggest that each sniffing cycle has the potential to represent detailed information about an odor and serve as a discrete coding unit: an odor snapshot. Behaviorally, independent olfactory samples might be useful components for higher order olfactory computations such as tracking an odor source or tagging odors to locations.

Electrophysiological evidence demonstrates that olfactory neural activity is strongly patterned by respiration and suggests that the phase of spiking relative to the sniff cycle might encode information about odor concentration and identity (Figure 5). Additionally, there are data showing that neurons across a diverse range of systems can couple to the sniff cycle. Therefore, the sniff cycle may be relevant for both the initial encoding as well as the process of integrating olfactory signals with cognitive and motor processes. We described two distinct phase-coding schemes for odor information (Figure 6) and two different ways in which phase encoding could support the dynamic coordination between the olfactory bulb and other areas (Figure 7). While at present, relatively little evidence exists to corroborate phase coding within the sniff cycle, it will be important to more systematically examine not only the firing rates of odor responses but also their temporal relationship to the sniff cycle.

If the notion of the sniff cycle as a fundamental unit for olfactory processing is supported by future studies, the functional implications may well extend beyond olfaction. A particularly significant implication of the kind of temporal chunking implied by sniffing is that it may give rise to discrete cognition: temporal chopping of perception, action, or thought (VanRullen and Koch, 2003). In light of this, the sniff cycle should provide a good model system for investigating the role of temporal chunking in the nervous system and its impact on neural coding, inter-areal coordination, and behavior.

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