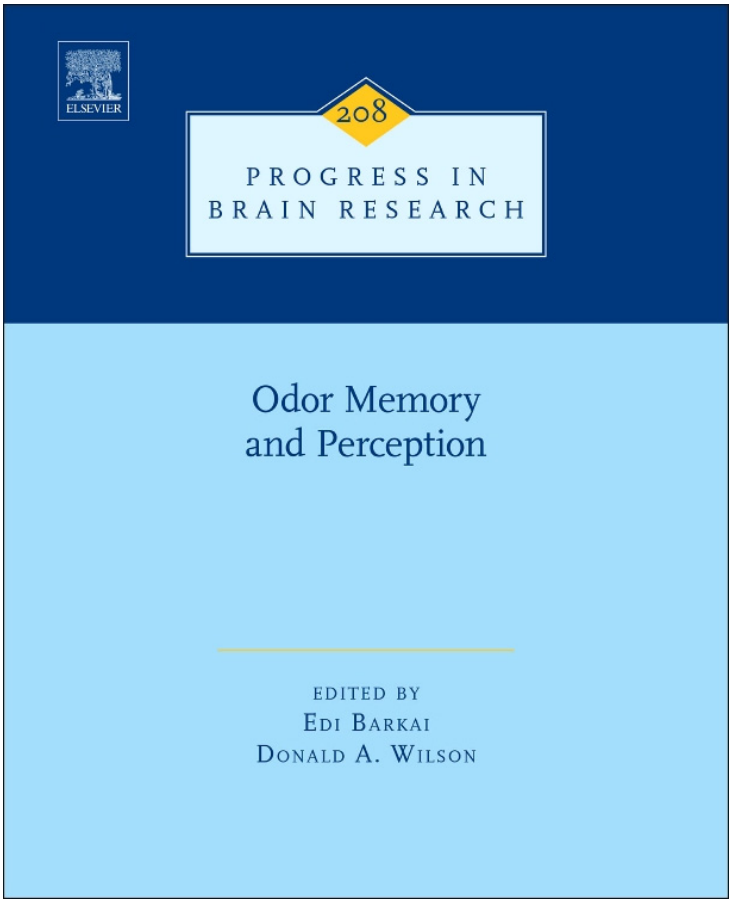

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CHAPTER

Circuit Oscillations in Odor Perception and Memory

9

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Abstract

Olfactory system neural oscillations as seen in the local field potential have been studied for many decades. Recent research has shown that there is a functional role for the most studied gamma oscillations (40–100 Hz in rats and mice, and 20 Hz in insects), without which fine odor discrimination is poor. When these oscillations are increased artificially, fine discrimination is increased, and when rats learn difficult and highly overlapping odor discriminations, gamma is increased in power. Because of the depth of study on this oscillation, it is possible to point to specific changes in neural firing patterns as represented by the increase in gamma oscillation amplitude. However, we know far less about the mechanisms governing beta oscillations (15–30 Hz in rats and mice), which are best associated with associative learning of responses to odor stimuli. These oscillations engage every part of the olfactory system that has so far been tested, plus the hippocampus, and the beta oscillation frequency band is the one that is most reliably coherent with other regions during odor processing. Respiratory oscillations overlapping with the theta frequency band (2–12 Hz) are associated with odor sniffing and normal breathing in rats. They also show coupling in some circumstances between olfactory areas and rare coupling between the hippocampus and olfactory bulb. The latter occur in specific learning conditions in which coherence strength is negatively or positively correlated with performance, depending on the task. There is still much to learn about the role of neural oscillations in learning and memory, but techniques that have been brought to bear on gamma oscillations (current source density, computational modeling, slice physiology, behavioral studies) should deliver much needed knowledge of these events.

Keywords

oscillation, gamma, beta, theta, olfactory bulb, hippocampus, coherence, piriform cortex, odor discrimination, respiration

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1 INTRODUCTION

The mammalian olfactory system produces an alphabet of rhythmic oscillations of the local field potential (LFP) and electrocorticogram/electroencephalogram (EEG) that track behavioral and cognitive processes associated with its many structures and modes. Cortical rhythms produce a spectrum of frequencies known as a 1/*f* power spectrum. In this type of spectrum, each successively higher frequency produces less power (amplitude) than the adjacent lower frequencies. This means that the signal itself will appear the same no matter what timescale is used, which is known as self-similarity. The olfactory bulb (OB) power spectrum contains significant and persistent deviations from this power falloff, showing elevated frequency band peaks where signals are more periodic than the irregular 1/*f* background activity (Fig. 1A). Some of these

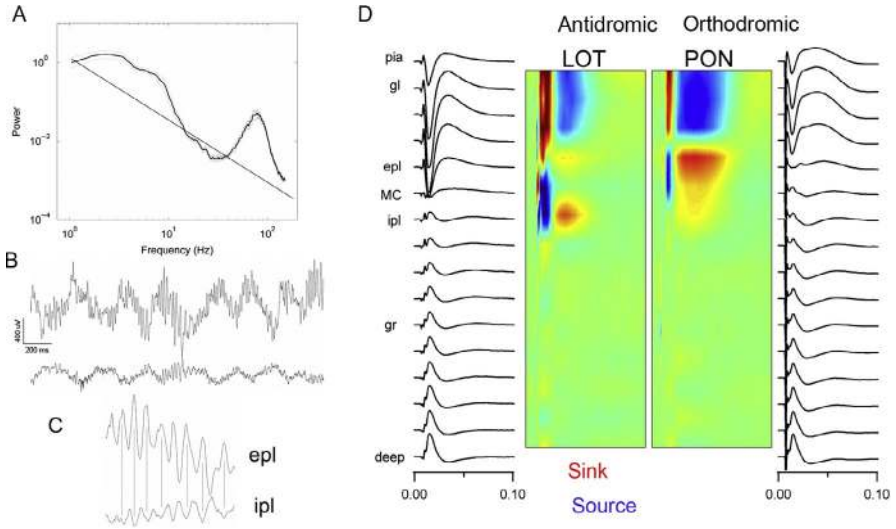

FIGURE 1

Spectral and spatial characteristics of the olfactory bulb LFP. (A) Power spectrum of waking activity from the olfactory bulb. Dashed line estimates the 1/*f* background. Note the deviations from this line in the respiratory (theta) and gamma ranges. (B) Simultaneously recorded LFP signals from superficial (top) and deep layers of the olfactory bulb. The signal is reversed across the layers. (C) Zoomed in portion of the signal in (B) showing the reversal of the fast oscillation across the cell layers. (D) Current source density estimates from evoked potentials in the olfactory bulb. Left side: lateral olfactory tract (LOT) stimulation antidromically stimulates the mitral/tufted cells and produces an oscillatory-evoked potential. Top: pial surface, bottom: mid-granule cell layer. Colored panel: current estimates from the adjacent LFP channels; current sinks are red, current sources are blue. Right side: primary olfactory nerve (PON) orthodromic stimulation.

oscillatory bands have been very well studied, others have only recently been described, but all are still objects of active investigation.

Soon after the first frequency descriptions of the EEG by Beck, Neminsky, Cybulski, Berger, and Jasper (1891–1938; reviewed in Ahmed and Cash, 2013) came Adrian's papers describing oscillations in the mammalian OB (Adrian, 1942, 1950). These fast oscillations were evoked in anesthetized hedgehogs, cats, and rabbits to many different odors. Around the same time were reported similar fast oscillations of the LFP in the human OB (Dodge et al., 1956). By the end of the 1950s, this effect had also been reported in waking cats and was then followed by many papers that have stood as foundational works on olfactory oscillations (Freeman, 1974a,b, 1975; Rall and Shepherd, 1968).

2 THE LFP IN THE MAMMALIAN OLFACTORY SYSTEM

The LFP represents the sum over a spatial average of many local neurons. Depending on the cortical area and size and impedance of the recording electrode, the number can vary from on the order of 100 to 10,000 neurons. The types of neuronal activity that contribute to this signal vary and must be studied separately, because each cortical area contains different neuronal circuits with different properties. In the mammalian OB, the main source of the LFP comes from granule cells, because of their parallel geometry (Freeman, 1972a, 1974a,b; Martinez and Freeman, 1984). However, the LFP also represents many other features of the neuronal types in the OB. The mitral and tufted cell firing patterns show relationships to the LFP that matches that of the granule cells with which they are closely connected. Intense study of the oscillatory potential evoked by stimulation of the lateral olfactory tract (LOT) and primary olfactory nerve (PON), coupled with computational modeling, gave us the first dissection of an oscillatory cortical circuit (Freeman, 1975; Rall and Shepherd, 1968). Using this methodology, several different phenomena were identified and connections predicted that in the intervening decades have been verified by others with modern methods. While the vast array of neuronal cell types was not known at that time, the basic predictions have all been verified.

One electrode cannot distinguish between signals produced locally and those produced in nearby areas picked up on the electrode via volume conduction. An easy method that is used in my laboratory and a handful of others can disambiguate between local and distant sources of the LFP. A cortical layer has geometry that produces a dipole field perpendicular to the cortical layers. Simply placing two electrodes on either side of the cortical layer, as close to perpendicular as possible, allows bipolar recording to discard or attenuate any signals that are not reversed across the two leads (Fig. 1B). Those that are reversed are the signals created by the local population. This method is not foolproof; if the placement is not perfect or the sources move around across different cortical layers, the resulting phase measurements and interpretations can be altered. Therefore, we often

use a monopolar recording but rely on the bipolar record to verify the source of a type of event.

To address questions involving the source of an LFP event, a more detailed analysis of the field is necessary. An extension of LFP analysis is current source density (CSD). This method uses a spatial derivative across voltage signals from electrodes in a linear array to identify the sources and sinks of current (Fig. 1C). An early study using this method allowed verification of modeling results that suggested that the fast odor-evoked oscillation originated from the reciprocal synapse between mitral and granule cells, among other findings. CSD has been used sparingly in the OB, but it has been used to greater effect in the PC circuit and in the hippocampus (Buzsaki et al., 1986; Leung, 1998; Rodriguez and Haberly, 1989). New technology has made practical the recording of many channels simultaneously in thin linear arrays, which means that the use of CSD should become more popular. While it is an old technique by innovative standards, the value of the data is impressive.

One criticism of using the LFP is that it averages over neurons and loses information. In one sense this is true, in another sense it is not. The loss of information can be seen when information is viewed as the spike events of individual neurons. This information is of course not present in the LFP signal. However, if enough is known about what the LFP signal represents relative to the underlying neuronal properties, the LFP can give more information than individual neurons. Because spiking is relatively sparse, it is difficult to tell if neurons' firing patterns are coherent with each other during a small period of time, such as a sniff bout or even a single sniff. Because the relationship between mitral/tufted cell spiking and the LFP is to a large degree known, it is possible to infer the level of local population cooperativity from the size of the LFP oscillation and the coherence between the spike and the local field. This gives information that recording many neurons simultaneously is unlikely to give.

3 OSCILLATORY BANDS IN THE OLFACTORY SYSTEM

Three major bands have been identified as having functional significance for olfactory processing in rats, mice, cats, and rabbits (frequency bands are for rats and mice): the theta or respiratory band (2–12 Hz), the gamma band (40–100 Hz), and the beta band (18–30 Hz). These bands are associated with specific types of behavioral events and have known relationships to each other. Theta oscillations track and represent respiratory behavior in the OB. Gamma oscillations are associated with local odor processing and neural precision, and they consist of two subbands which have different associations with olfactory and respiratory behavior. Beta oscillations emerge with odor learning and odor sensitization, and relatively little is known about their functional roles.

In the following sections, I will discuss each oscillation type in detail, starting first with phenomenology, moving on to the circuit properties that produce

the oscillation, and finally ending with what is known about the functional role of the oscillation and the future directions for research.

3.1 Theta

3.1.1 Phenomenology

Olfaction in mammals begins with breathing and so does the range of oscillatory events in waking mammals' OBs. Theta oscillations only recently were named such, noting that their frequency band in rats and mice (2–12 Hz) overlaps to a large extent with theta oscillations in the hippocampus. These oscillations have for most of their scientific history been labeled respiratory oscillations because that is what they represent. Mostly anecdotal reports have linked this oscillation to the respiratory cycle. However, the anecdote is powerful and convincing (Fig. 2A and B). These waves were first described in the late 1950s (Ottoson, 1958, 1960), and in the first years of study, much was made of determining that they were indeed brain potentials and not movement artifacts from breathing. Principal neurons in the OB can show firing patterns that are locked to the inhalation cycle; about 50% of mitral/tufted cells recorded in waking rats and other mammals show phase locking to the respiratory wave (Bhalla and Bower, 1997; Cattarelli et al., 1977; Pager, 1985; Ravel and Pager, 1990; Fig. 2C). When rats sniff at high rates, locking of individual neurons to the respiratory cycle is significantly reduced, but the respiratory wave remains (Bhalla and Bower, 1997; Kay and Laurent, 1999). Whether the theta rhythm is coherent with respiratory activity at all sniffing frequencies is unknown. Studies addressing this have been conducted only at low respiratory rates.

Changes in behavioral state can result in changes of respiratory activity and therefore the respiratory rhythm, and these changes may also affect the way in which the respiratory activity is carried by other brain regions which receive significant input from the OB. Under anesthesia, there is significant coupling between the OB and PC respiratory rhythms, but this coupling is not constant. Light ketamine anesthesia reduces the coupling at respiratory rhythms between the OB and PC, while deeper anesthesia maintains strong coupling (Fontanini and Bower, 2005). During fast- and slow-wave activity states (FWA and SWA, respectively), which mimic sleep states under urethane anesthesia, low-frequency activity in the PC shows variable coupling with the OB and higher order areas (Wilson and Yan, 2010). During SWA, the PC is more strongly coupled with low-frequency activity originating in the hippocampus and less sensitive to incoming olfactory stimulation, while during FWA the PC is more strongly coupled with the OB and more sensitive to incoming olfactory stimulation.

3.1.2 Circuits

Olfactory signals are delivered to the OB from the sensory epithelium via the olfactory nerve. Because respiration delivers the sensory stimulus to the olfactory receptors in rhythmic fashion, it is reasonable to expect that sensory information is delivered with each sniff in a packet-like fashion to the OB. Recent work suggests

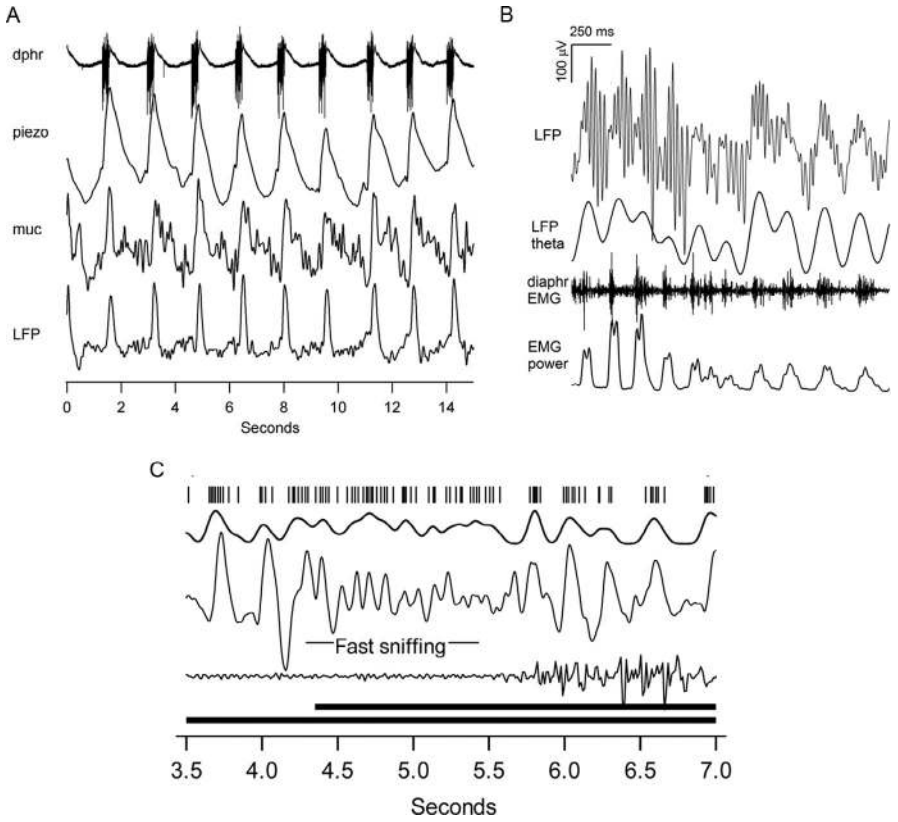

FIGURE 2

Respiratory activity in the olfactory bulb. (A) From top to bottom: diaphragm EMG, airflow in front of the nose (piezo), olfactory mucosa population activity, and LFP from the OB in a urethane anesthetized rat. Signals show the strong coherence of the signal across modalities. (B) From top to bottom: OB LFP, filtered theta band from the LFP (low pass filter at 12 Hz), diaphragm EMG, and rectified and smoothed EMG signal showing coherence in a waking rat sniffing in the home cage. (C) From top to bottom: M/T cell spike raster, smoothed spike train, theta band signal from the OB LFP, lick signal, odor, and light during an operant trial. During the slower breathing periods, the M/T cell fires a burst with each inhalation. During fast sniffing, the M/T cell uncouples from the respiratory signal.

Panel (C): From Kay and Laurent (1999).

that olfactory receptor neurons in the sensory epithelium are also activated by the mechanical stimulation from airflow, which can effectively boost a receptor neuron's weak response to an odor stimulus (Grosmaitre et al., 2007). Once this respiration-gated signal reaches the OB, what circuits are responsible for its strong representation in single unit and field recordings? Are these respiratory-gated signals

simply driven by the sensory input or are mechanisms intrinsic to the OB at work as well? The most likely answer is that both processes are involved. Studies at multiple levels, including computational modeling, suggest that respiratory oscillations in the OB are both produced by glomerular circuits which process the incoming stimulus volley and induced in OB neurons by the olfactory nerve. Early work by Freeman suggested that the rise in excitation associated with sensory input is driven in part by the olfactory nerve input but also facilitated by glomerular circuitry (Freeman, 1974a,b; Martinez and Freeman, 1984). Having little information regarding the later described diversity of glomerular neuronal cell types, he hypothesized that boosting and entrainment of sensory input in the OB were accomplished by mutually excitatory action between GABAergic periglomerular cells in the glomerular network. This hypothesis was supported by several sets of experimental and modeling results. CSD analysis of OB-evoked potentials using PON stimulation revealed an excitatory current in the glomerular layer that was not completely accounted for by the geometry of incoming sensory information (Martinez and Freeman, 1984). Modeling suggested an excitatory current in the glomerular network to resolve the experimental results (Freeman, 1975). Periglomerular cells were shown to accumulate Cl^- in portions of the glomerular layer, and accumulation of Cl^- could reverse the action of GABA at $GABA_A$ receptors (Siklos et al., 1995). Research has since revealed multiple excitatory processes in the glomerular layer, including mutual excitation among mitral cells within a glomerulus and excitatory action of external tufted cells across glomeruli (Hayar et al., 2004).

Mitral and tufted cells are usually grouped together in research on waking rodents, simply because it is difficult to discern the cell type when recording extracellularly. Two recent groundbreaking studies have shown that these two cell types, which have different projection patterns to higher order areas, receive sensory input differently, fire at different phases of the respiratory rhythm, and are regulated differently as respiratory frequency changes. Sensory neuron axons directly excite tufted cells, and mitral cells receive this input indirectly through external tufted cells (Gire et al., 2012). Tufted cells fire early in the inspiration period, with little phase change with concentration increase, and mitral cells fire in late inspiration and show phase advances with concentration increases mediated by local inhibition (Fukunaga et al., 2012). Thus, the two projection pathways of these neuronal types should be activated in different phases of a sniff, with more rostral regions, including the olfactory tubercle, in the early period by tufted cells and more diffuse regions in the later period by mitral cells.

Respiratory activity is not confined to the input stimulus; some studies have suggested that there is significant centrifugal involvement in the respiratory driving of OB neurons (Ravel et al., 1987). There are brainstem and midbrain respiratory circuits which could impinge on OB activity via the ventral hippocampus and other limbic areas. In addition, most areas of the basal forebrain have neurons that fire in phase with respiration (Manns et al., 2003), and these areas project widely to the OB and other olfactory areas.

3.1.3 Function

What might be the function of the respiratory rhythm? We will assess this by looking for evidence that respiratory oscillations are associated with specific neural and perceptual consequences. At the behavioral level, rats and mice show a range of respiratory frequencies, but they sort into about two categories in waking states. Low respiratory rates (2–4 Hz) are associated with resting and immobile states, and high respiratory rates (5–12 Hz) are associated with exploration and odor sniffing in discrimination behavior. These markedly different but stereotyped respiratory states match two types of plasticity in piriform cortex neurons. When input to PC pyramidal cells is simulated to mimic mitral/tufted cell firing during fast sniffing, the pyramidal cells follow increases in firing in a linear fashion. When the input is simulated from OB activity during slow breathing, the PC neurons respond robustly to the onset and the synapses depress quickly (Oswald and Urban, 2012). The short-term depression is overcome by early activation during fast sniffing but has a significant effect during slower respiratory rates. This suggests that the neurons, circuit, and behavior are tuned to transfer odor information to cortex when it is needed. This two-state mode of transfer is reminiscent of thalamocortical interactions in burst (slow wave) and tonic (fast wave) states (Kay and Sherman, 2007; Sherman, 2001).

The phase of respiration can be used to address higher order activity in the OB. In rats exposed to odors in an appetitive conditioning paradigm, mitral/tufted cells fire on specific odor-associated phases of sniffs during later parts of long odor exposures (Pager, 1983), and these phase specificities change over days (Bhalla and Bower, 1997). A more recent study has confirmed that ensembles of mitral cells "tile" the sniff so that the group of neurons together represents information across the entire sniff (Shusterman et al., 2011).

Does the sniffing rhythm connect with similar rhythmic processes in other sensory systems? If so, then this might be one mode of sensory coupling in multisensory processing. Recent studies in the rat whisking system have addressed this and found that whisking and sniffing are coherent during fast sniffing, but not during slower breathing periods, in rats and mice (Moore et al., 2013).

The respiratory rhythm overlaps in frequency with theta rhythms in the hippocampus and elsewhere. The frequency similarity between the OB respiratory rhythm and hippocampal theta waves is compelling, and the question of coordination between these two rhythms is an obvious one. If they occupy similar frequency ranges and are so closely connected, are OB and hippocampal theta oscillations related? The answer to this is usually no. While the frequencies are similar, there is no consistent phase relationship between the two rhythms. Two studies have described specific circumstances where this is not the case. The first addressed the respiratory rhythm itself and its relationship to the hippocampal theta rhythm (Macrides et al., 1982). Rats were trained to do a go/no-go odor discrimination, and sniffing and hippocampal LFP were recorded. At the point of learning the first association and performing at high levels, there was no consistent phase relationship between the sniff cycle and hippocampal theta. However, when contingency relationships were reversed for the

two odors (reversal learning), the phases for the two rhythms were then consistent during early learning and fell off as learning progressed. This study was done before coherence measures were easily done and popularly used, but the phase relationship suggests that the signals were coherent and that the coherence magnitude was negatively correlated with learning. In a more recent study, we showed that theta oscillations were modestly coherent between the OB and hippocampus during learning of a relatively difficult odor identification task that required the rats to keep track of the intertrial timing. More importantly, the magnitude of coherence between these two areas was linearly and positively related to the learning level (Kay, 2005; Fig. 3). Thus, in these two cases, respiratory activity was coherent with hippocampal theta during the learning process. What function this coherence serves in the learning process is open to speculation, but it may be a mechanism for including or excluding the hippocampus from olfactory processing or the olfactory system from hippocampal processing in an as-needed basis.

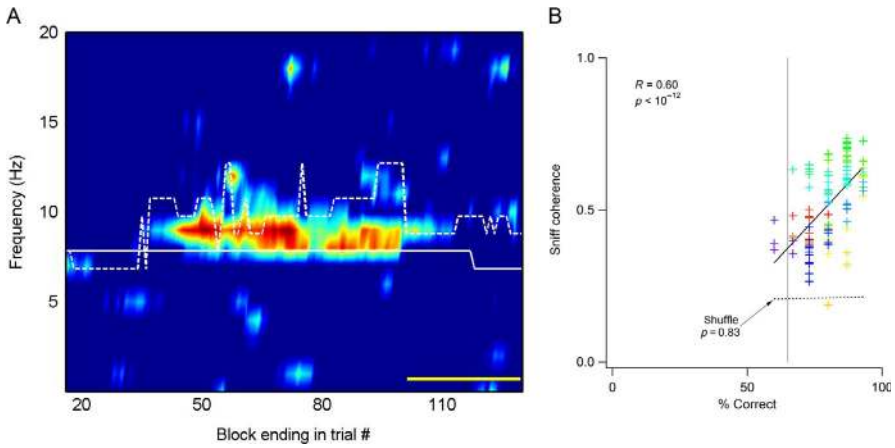

FIGURE 3

Coupling between OB theta/respiratory signal and dorsal dentate gyrus theta band during odor discrimination. (A) Coherence spectrum from trial blocks in an operant odor discrimination session (red color indicates high coherence). Solid white curve shows hippocampal theta peak frequency in the 6–13 Hz band; dotted curve shows OB peak frequency in the same band. Yellow bar on right bottom indicates period of the session in which there was no discrimination; only the CS+ was delivered with reward for response. In this task, the rats had to keep track of the 6 s intertrial interval, where every other trial was blank (effectively a 12 s intertrial interval). Responding (lever press) between 0.5 s before and 0.5 s after odor stimulus delivery disabled the reward for that trial. For details on task and results see Kay (2005). (B) Correlation between theta coherence and performance in trial blocks. Colors indicate time in the session, with blue early and red late.

There are still open questions regarding the circuitry and function of the theta respiratory rhythm in the olfactory system. The degree to which respiratory rhythms and OB theta are coherent at all respiratory frequencies is unknown. If there are privileged frequencies for respiration that take advantage of the more central brain rhythms and similar rhythmic processes in other sensory systems, what does this mean about animals that sniff at lower frequencies, such as humans? Are there still mechanisms for coupling these areas for sensory and cognitive purposes?

3.2 Gamma

3.2.1 Phenomenology

The odor-evoked oscillations described by Adrian have been seen in every mammalian species so far studied (Adrian, 1942, 1950; Bressler and Freeman, 1980; Fig. 1) and remain one of the most studied oscillatory events in the mammalian brain (Rojas-Líbano and Kay, 2008). While the frequency changes dependent on the species (Bressler and Freeman, 1980), the framework and circuit remain the same across mammalian species. This same phenomenon has been identified in several non-mammalian vertebrate species, including zebrafish and frogs, where the fast oscillations range from 10 to 30 Hz (Kay and Stopfer, 2006). Even more striking is the similarity of odor-evoked oscillations in many insect antennal lobes and the limax procerebrum (Delaney et al., 1994; Laurent and Davidowitz, 1994; Laurent et al., 1996; Stopfer et al., 1997; Tanaka et al., 2009), and these oscillation frequencies range between less than 1 and 30 Hz.

In mammals, odor-evoked gamma oscillations arise at the end of inhalation at the transition to exhalation. While the phase relationship is quite robust, the amplitude and frequency distribution of these bursts can be quite variable (Fig. 4A–C). Furthermore, the gamma band activity can become irregular during fast sniffing when rabbits and rats are sniffing odors that they know quite well (Freeman and Schneider, 1982; Kay, 2003; Fig. 4E).

A second type of gamma oscillation has been noted in a few studies, termed gamma 2 in one study (with the classic sensory-evoked gamma termed gamma 1) (Bressler, 1988; Kay, 2003; Manabe and Mori, 2013). This slow gamma has been observed at the end of inhalation and also during interbreath periods when a rat is alert and motionless and also while grooming (Fig. 4D and E). These oscillations are also seen in the later part of long gamma events in the OB, as exhalation proceeds. In this chapter, the term "gamma" refers to gamma 1, and "low gamma" refers to gamma 2.

3.2.2 Circuits

The mammalian OB circuit resembles closely the OBs of the non-mammalian vertebrates, suggesting that the species share a common mechanism for fast, odor-evoked oscillations of the circuit as exhibited in at the population level. The invertebrate organisms in which odor-evoked fast oscillations have been observed have similar circuits that may have evolved independently (Eisthen, 2002). The

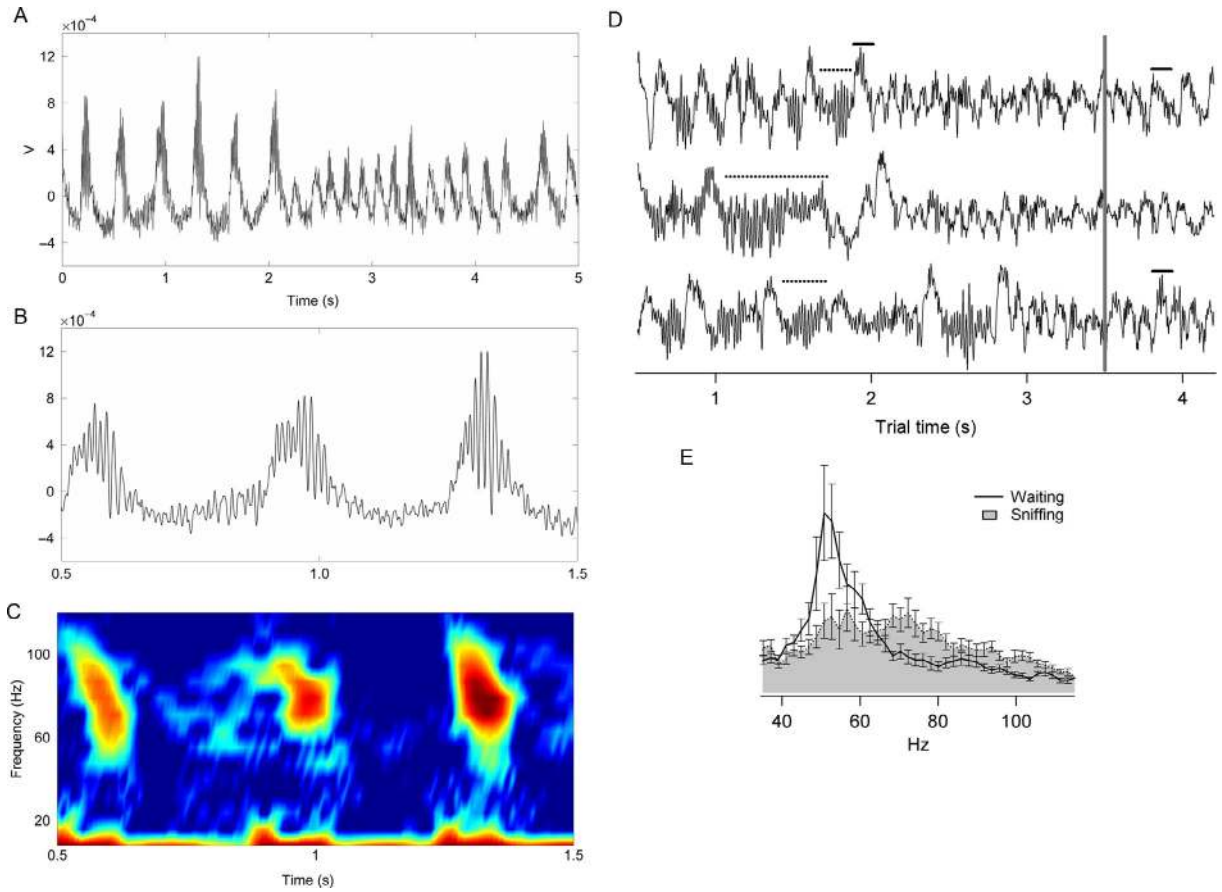

FIGURE 4

Gamma oscillations in the olfactory bulb. (A) Five seconds of LFP from a rat OB during waking spontaneous behavior, note spontaneous changes in theta respiratory rhythm and amplitude. Gamma bursts initiate at the peak of inhalation. (B) One second of LFP zoomed from (A). Gamma bursts start at lower amplitude and higher frequency and then slow down. Also note weak lower frequency gamma (low gamma/gamma 2) just before the second inhalation period. (C) Spectrogram from data in (B). Note the sweep-like form of the gamma bursts from high to low frequency. (D) Three segments of data from a prestimulus period in an operant task marking long segments of low gamma activity. (E) Gamma band power spectra from prestimulus (low gamma/gamma 2 peak) and odor sniffing period (broad gamma band).

Panel (E): From Kay (2003).

reciprocal dendrodendritic synapse between mitral/tufted cells and granule cells is responsible for this oscillation in vertebrate olfactory systems, although much more is known about the mammalian gamma oscillation circuit than non-mammalian vertebrate species. Many decades of work have contributed to knowledge of the mammalian circuit, much of which is summarized in Rojas-Líbano and Kay (2008).

What are the primary pieces of evidence that support the dendrodendritic synapse as the mother of gamma oscillations? The evidence is drawn from many types of analysis: OB slice physiology, genetic deletion studies, CSD, and computational modeling. Many studies at the slice level have addressed the gamma oscillation. Intracellular recordings of mitral cells show subthreshold gamma oscillations that are blocked when inhibition onto those neurons is blocked (Lagier et al., 2004). Granule cell action potentials are not required for gamma oscillations. CSD analysis identified paired sources and sinks of current in the external and internal plexiform layers associated with gamma oscillations in anesthetized rats (Neville and Haberly, 2003). A much earlier study addressed the sources and sinks of characteristic oscillatory waveforms produced in response to electrical stimulation of the LOT or the PON (Martinez and Freeman, 1984). Physiological and modeling studies based on the oscillatory-evoked potential also informed the reciprocal synapse's involvement in gamma oscillations (Freeman, 1972b, 1975; Rall and Shepherd, 1968).

NMDA and AMPA receptors have interesting effects at the reciprocal synapse, and modeling studies conflict regarding which of these receptor types is most responsible for gamma frequencies (Bathellier et al., 2006; Chen et al., 2000; Schoppa, 2006). Two main scenarios emerge: (1) GABA release is supported by NMDA receptors on spiking granule cells (Chen et al., 2000), and coincident input at gamma frequency near granule cell bodies can release the Mg^{2+} block on NMDA receptors allowing release of GABA to drive gamma oscillations (Halabisky and Strowbridge, 2003). (2) Gamma oscillations are supported by AMPA receptors on granule cells, which are fast and gate activation of inhibition into small time packets (Schoppa, 2006); this allows graded release of GABA in the absence of spiking.

Early computational modeling examined olfactory system dynamics. The original computational work on OB and piriform cortex oscillations, by Shepherd and Freeman, addressed the oscillatory-evoked potential produced by electrical stimulation of the LOT (Freeman, 1964; Rall and Shepherd, 1968). More recent studies have looked at simpler and more complex analyses of how the circuit can produce gamma frequency band oscillations, based on physiological work in brain slices and insect brains, examining the properties of principal neurons and receptor time constants (e.g., Bathellier et al., 2006; Bazhenov et al., 2001; Brea et al., 2009; Lagier et al., 2007). Another computational perspective treats mitral/tufted cells as individual, somewhat desynchronized, oscillators and addresses gamma oscillations at the level of the LFP as a product of synchronized activity in large numbers of these individual oscillators in which correlated noisy inputs from granule cells synchronize mitral/tufted cell oscillations, which in turn synchronize the noisy inputs from granule cells (Galán et al., 2006; Marella and Ermentrout, 2010). All of this attention at

both the physiological and computational levels makes the OB gamma oscillation one of the most studied cortical oscillations in the mammalian brain.

If the primary mode of transferring information between brain regions is via action potentials, what do gamma oscillations represent in terms of neuronal firing statistics? Mitral/tufted cells show a relationship with the LFP that describes the gamma oscillation. If the probability of firing is computed relative to the LFP, a gamma oscillation waveform is returned (Eeckman and Freeman, 1990; Freeman, 1968a, 1968b; Fig. 5). Spike-field coherence is a modern representation of the pulse probability density used in early studies. When gamma oscillations get larger, there is

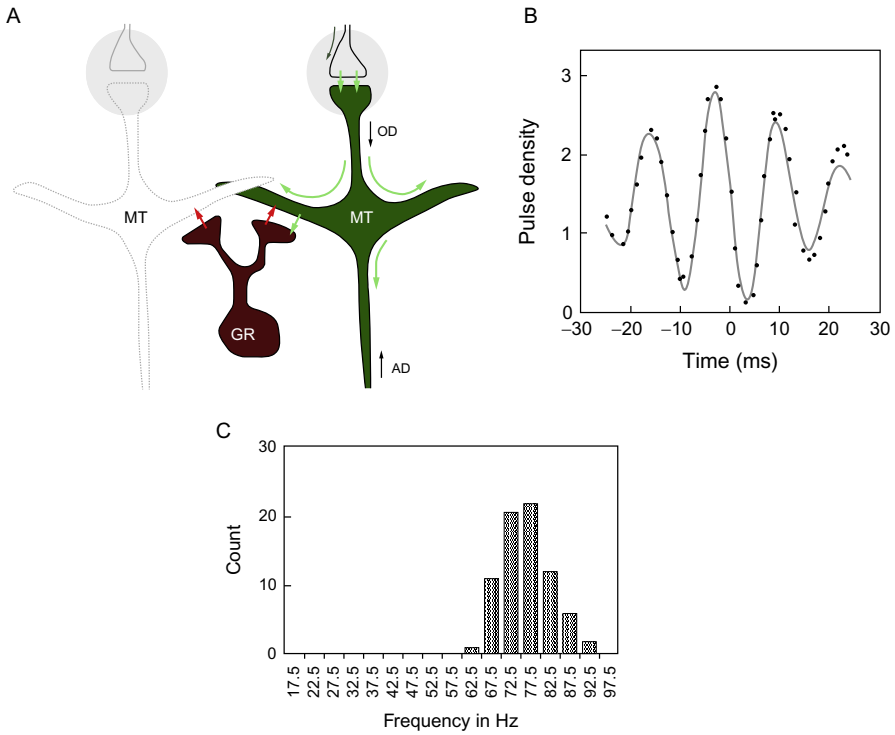

FIGURE 5

Gamma oscillation circuit and pulse statistics. (A) Circuit that drives gamma oscillations in the OB is the reciprocal dendrodendritic synapse between GABAergic granule cells and glutamatergic mitral and tufted cells. (B) Pulse probability density of multiunit activity based on the LFP signal returns the gamma oscillation. The gamma oscillation represents the probability of spiking from M/T cells in the neighborhood. (C) Frequency distribution of many recordings returns the gamma frequency band.

Panel (A): From Rojas-Líbano and Kay (2008), used with permission. Panels (B) and (C): From Eeckman and Freeman (1990), used with permission.

higher firing precision among the population of neurons, which means that increases in gamma power can be interpreted as increases in local firing precision (Gray and Skinner, 1988; Nusser et al., 2001; Fig. 6). The beta3 knockout mouse is missing the beta3 subunit of the $GABA_A$ receptor and has nonfunctional $GABA_A$ receptors on OB granule cells (Nusser et al., 2001). This means that these inhibitory neurons cannot be inhibited either by local GABAergic neurons or by GABAergic input from the basal forebrain or elsewhere. Beta3 knockout mice have extremely large gamma oscillations, and mitral cells show strong coupling with gamma frequency membrane oscillations without higher firing frequencies. These results suggest that inhibition of the granule cells helps to desynchronize the OB network. This may be important to keep the circuit in a stable oscillatory range because beta3 mice are prone to seizures.

Changes in gamma oscillation power associated with higher coherence between M/T spikes and the LFP gamma oscillation may inform the circuits of downstream areas, because piriform cortex neurons are triggered by a few spikes arriving in a very short time window (5–10 ms) (Franks and Isaacson, 2006). Because large gamma

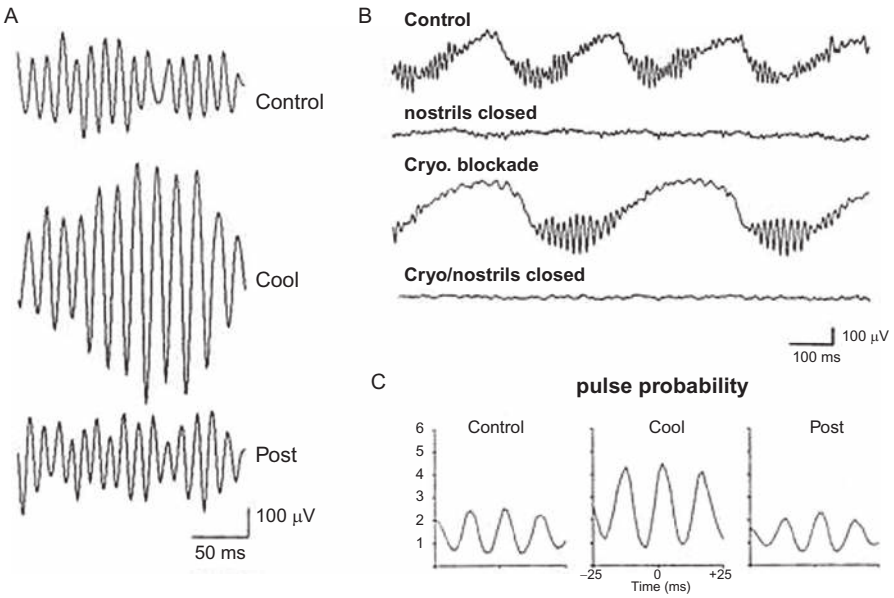

FIGURE 6

Olfactory bulb gamma oscillations increase in power when centrifugal input is turned off. The olfactory peduncle of a rabbit was cooled to temporarily prevent centrifugal activity from reaching the OB. (A) The gamma oscillation increases in amplitude when the cooling is on and returns to the less regular baseline when cooling is off. (B) Longer segments of LFP in both conditions. (C) Pulse probability density (as in Fig. 5) during control, cooling, and post cooling periods. M/T cell firing is more strongly locked to the gamma oscillation without centrifugal input.

From Gray and Skinner (1988), used with permission.

oscillations show us that the M/T cell spikes are grouped more tightly into small time windows, this implies that it is more likely that a few M/T cells will send spikes to a PC neuron in a short time window causing the PC neuron to fire.

In insect systems, a similar synapse between projection neurons and local neurons supports fast odor-evoked gamma-like oscillations. Intracellular recordings in local and projection neurons show subthreshold oscillations in the 20 Hz range, evoked by odor stimulation (Laurent and Davidowitz, 1994). These same oscillations can be measured at the level of the LFP from the mushroom body, one of the downstream areas that receive projection neuron input. Although not the same frequency as gamma, these oscillations rely on the analogous synapse and are evoked by odors. If inhibition is blocked in the antennal lobe by application of picrotoxin, a $GABA_A$ antagonist, then there are no odor-evoked oscillations (MacLeod and Laurent, 1996). However, slow temporal firing patterns remain the same (MacLeod et al., 1998; Fig. 7). This means that individual neurons continue to fire with the same slow temporal structure, but their fine temporal structure is no longer coordinated. Under this treatment, responses of downstream neurons are altered as well, suggesting that oscillatory coordination is necessary for driving downstream neurons. During a fast oscillation, projection neurons fire on identified cycles of the fast oscillation so that a group of neurons represents the odor across the oscillation (Wehr and Laurent, 1996). A similar phenomenon may happen in the mammalian OB under anesthesia. One study has shown that individual mitral/tufted cells lock with local gamma oscillations differentially during exposure to different odors (Kashiwadani et al., 1999).

3.2.2.1 Coherence and Phase of Gamma Within a Cortical Area

The gamma oscillation recorded at many places in the OB shows high coherence within bursts, both in anesthetized and in waking mammals (Freeman and Schneider, 1982; Fig. 8A). However, the relative phase between two locations on successive bursts is random (Freeman and Baird, 1987). Because of this, coherence measured on a long sequence of bursts is severely underestimated due to random fluctuations in the phase relationship across the two locations (Kay and Lazzara, 2010). Therefore, spike-field coherence or the spiking probability associated with the LFP is computed from electrodes at or near same location in the OB. Gamma oscillations within the PC are also coherent, and the phase relationships are constant, following the input pathway from the LOT (Freeman and Baird, 1987).

3.2.2.2 Local Generation of Gamma Oscillations

Gamma oscillations appear to be a relatively local phenomenon within each cortical area, although they can show periods of high coherence between areas. The evidence for this comes from a few studies that cut central input to the OB and OB input to the PC and other areas. Cutting central input to the OB temporarily, by cooling or injecting lidocaine in the olfactory peduncle, or permanently, by cutting the feedback pathway at the level of the olfactory peduncle, causes gamma oscillations in the OB to increase dramatically (Gray and Skinner, 1988; Martin et al., 2004a, 2006; Fig. 6). These results suggest that the gamma oscillation is produced locally in the OB and

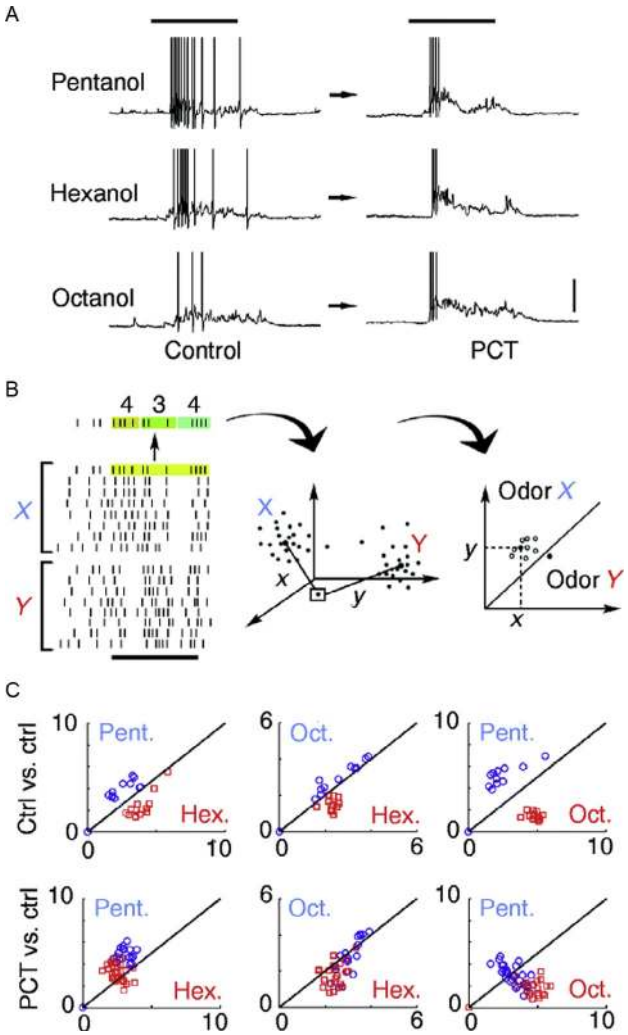

FIGURE 7

Insect gamma-like oscillations coordinate antennal lobe projection neurons and drive differences in odor-evoked firing patterns in downstream beta lobe neurons. (A) Locust beta lobe neurons that receive input from the antennal lobe projection neurons change their firing patterns when antennal lobe oscillations are blocked with picrotoxin. (B) Spike rasters from a single neuron are subjected to a distance metric that can discriminate between two odors (*x* and *y*). When the rasters are different, the clusters of points lie off the diagonal indicating that the rasters can be used to discriminate odors. (C) Comparison of beta lobe neuron spike raster clusters in control and picrotoxin conditions. In the picrotoxin condition, the clusters do not separate.

From MacLeod et al. (1998), used with permission.

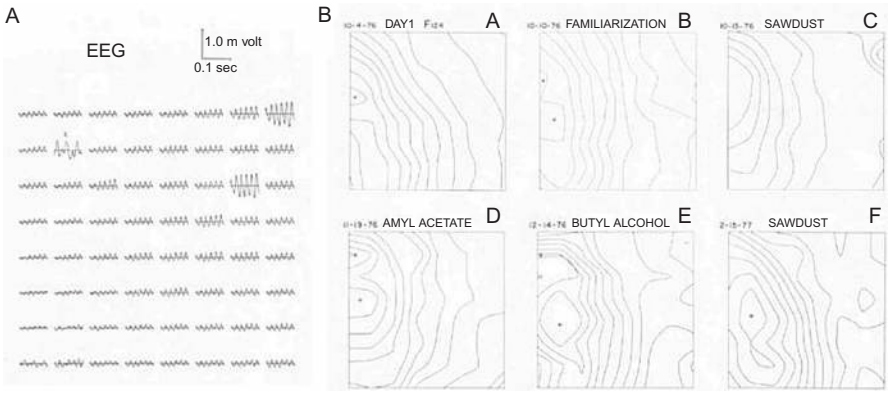

FIGURE 8

Gamma oscillations are coherent across a wide area of the olfactory bulb. (A) Signal recorded simultaneously from a 4 × 4 mm array of 64 electrodes on the surface of the rabbit olfactory bulb. Note that the signal is very similar across the electrodes (except for a bad channel in row 2 column 2). (B) Spatial pattern of the waveform amplitude in several conditions shows that the amplitude pattern can be used to discriminate odors and conditions (bad channel was replaced with the average from 2 adjacent channels). The pattern changes over days with familiarization to the apparatus (A and B). Response to sawdust is significantly different from background (C). Conditioning to amyl acetate and butyl alcohol show different patterns (D and E). After conditioning, the response to sawdust is dramatically changed (F).

From Freeman and Schneider (1982), used with permission.

that centrifugal input serves to desynchronize the local activity. This input comes in primarily onto granule cells, so central drive to the inhibitory network interferes with reciprocal interactions between mitral and granule cells. Cutting OB input to the PC by cutting the LOT results in a loss of the oscillatory component of the PC-evoked potential produced when a shock stimulus is applied to the stump of the olfactory tract leading into the PC (Freeman, 1968a,b). As the parameters of the oscillatory-evoked potential inform parameters of the gamma oscillation circuit, this means that cutting the OB input to the PC knocks out the gamma oscillation. This does not mean that the OB drives the gamma oscillation in the PC. If the missing OB input is replaced by tetanic stimulation at a low level on the remaining olfactory tract, the oscillatory response to the original shock stimulus returns. What this means is that OB input puts the PC network into the proper excitatory state to produce gamma oscillations. The same effect was seen in the entorhinal cortex after the LOT was cut (Ahrens and Freeman, 2001).

Low-frequency gamma oscillations are known primarily phenomenologically, although we have some hints of the circuits responsible. The beta3 knockout mice have no discernible low gamma oscillations, suggesting that local inhibitory circuits may drive the low-frequency gamma oscillation (Kay, 2003). Another hypothesis addresses the two populations of principal neurons and maps fast and slow gamma

onto the respiratory cycle, suggesting that the fast and slow gamma oscillations may be engaged by the tufted and mitral cells, respectively (Manabe and Mori, 2013). Because tufted cells fire early in the respiratory cycle, at the end of inhalation driven directly by sensory input, these were assigned to gamma oscillations, and the mitral cells, which fire with more variability and later in the respiratory cycle, were assigned to low gamma oscillations. Because the two types of cells project to somewhat different circuits (tufted to the olfactory tubercle and mitral to the entire olfactory system and parts of the limbic system), the hypothesis is that the two oscillations engage different functional processes.

3.2.3 Function

While some oscillations change or are completely eliminated under anesthesia, the gamma oscillation in the OB is arguably one of the more stable phenomena in neurophysiology. The historic studies were done under anesthesia, and Adrian experimented with many odors in the laboratory, including cigarette smoke! Later work showed that the state of anesthesia affects the oscillatory properties of this circuit, with deep pentobarbital anesthesia reducing the gain of the cortical area such that multiunit spiking is not easily induced by increases in voltage (Freeman, 2000). Under anesthesia, the circuit may resemble the simpler insect system (Kashiwadani et al., 1999), but in waking mammals, the story is much more complex. Gamma oscillations are modulated by behavioral state, the animal's personal history, and other factors (Kay, 2003).

Freeman took advantage of the waveform similarity across the OB during gamma oscillations to uncover an interesting dynamical principle. Amplitude estimates of the common waveform in the gamma band show a stable two-dimensional pattern of activation associated with normal breathing without odor stimulation (Freeman and Schneider, 1982; Viana Di Prisco and Freeman, 1985; Fig. 8). When odor associations were learned, new patterns associated with those odors and their associations emerged while the subjects sniffed the odors. All patterns were not permanent, but evolved slowly over time to new patterns, as the subjects gained more experience. Each new learned pattern changed the other patterns abruptly, and a change to an association also changed the patterns. Thus, it seems that the bulb maintains a dynamical phase space of activation patterns associated with meaning, which could be termed attractor states. These studies were the first in a series of clues that the gamma oscillation plays a special functional role.

Two studies, using honeybees and mice, addressed the functional role of gamma oscillations using large manipulations of the olfactory network. Picrotoxin was used to silence the inhibitory network in the honeybee antennal lobe ablating fast odor-evoked oscillations interfering with honeybees' discrimination of closely related odorants (fine odor discrimination) (Stopfer et al., 1997; Fig. 9A). Their discrimination of less similar odorants (coarse odor discrimination) was unchanged. Beta3 mice have significantly larger gamma oscillations than their littermate heterozygous controls, and they are better at fine odor discrimination than controls (Nusser et al., 2001; Fig. 9B). A third study tested changes in gamma oscillation power during fine versus

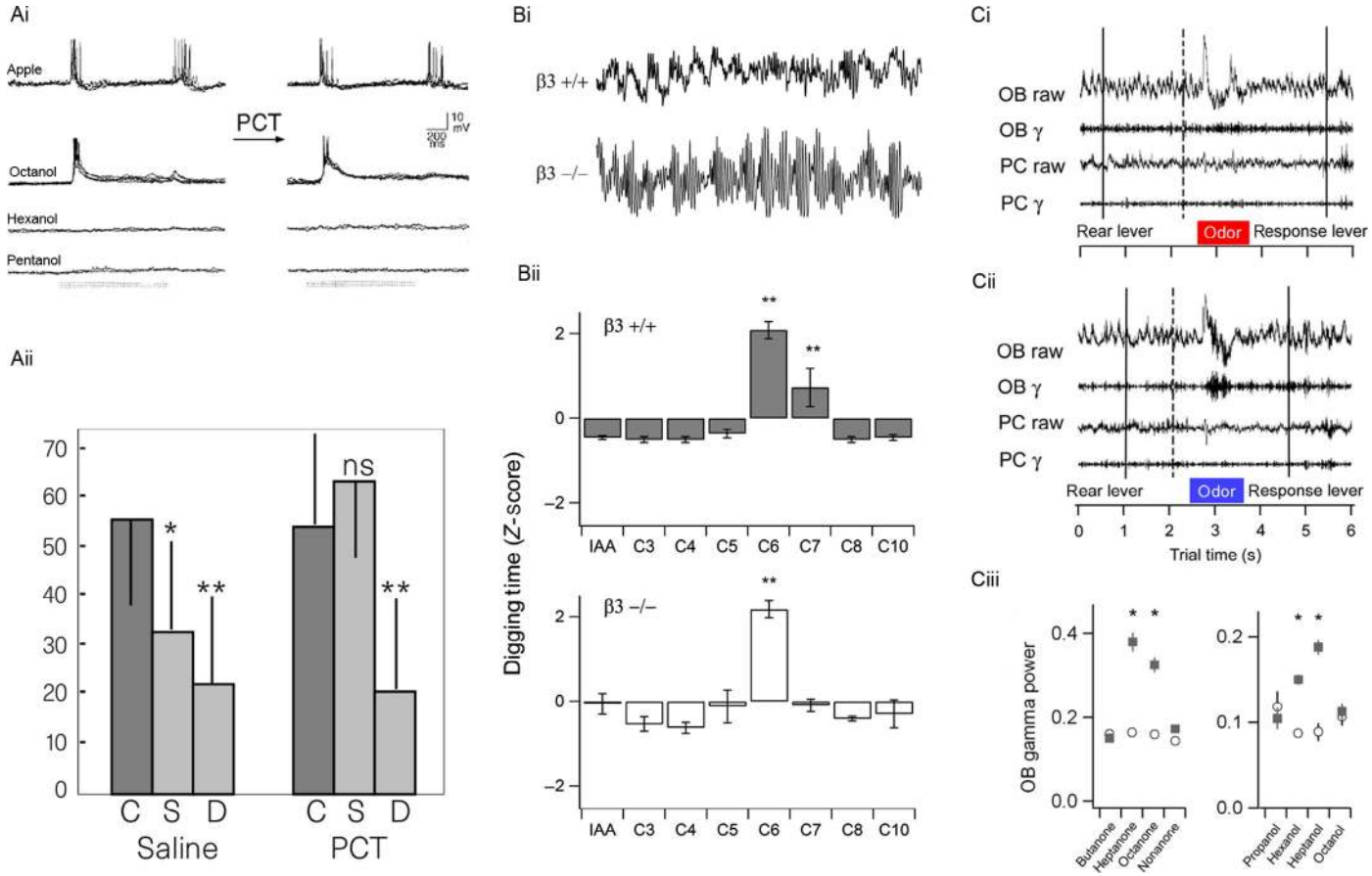

FIGURE 9

Gamma oscillations support fine odor discrimination. (Ai) Honeybee antennal lobe gamma-like oscillations disappear in the presence of picrotoxin. Projection neurons maintain their slow temporal firing patterns. (Aii) Control-treated honeybees show a response to the conditioned odor (C), but discriminate the similar (S) and different (D) odors. Picrotoxin-treated bees do not discriminate the similar odor but do discriminate the different odor. (Vertical scale shows the percent proboscis extension response; * $p < 0.05$, ** $p < 0.01$ in comparison to C. (Bi) Beta3 knockout mice have significantly enhanced gamma oscillations. (Bii) Control mice conditioned to hexanol (C6) generalize their response to heptanol (C7); knockout mice do not show normal generalization responses (** $p < 0.01$ compared to IAA control response). (Ci) Example data from an odor discrimination task in which rats discriminated very different/coarse (red, Ci) or very similar/fine (blue, Cii) odors. Note that gamma oscillations are enhanced during odor sampling in the fine discrimination condition. Vertical dashed line shows the estimated time of odor arrival. (Ciii) Group statistics show that fine odor discrimination boosts gamma power in the OB (* $p < 0.05$ comparing criterion to naive gamma. Solid squares- criterion; open circles- naive).

Panel (A): From Stopfer et al. (1997), used with permission. Panel (B): From Nusser et al. (2001), used with permission. Panel (C): From Beshel et al. (2007), used with permission.

coarse odor discrimination in rats (Beshel et al., 2007; Fig. 9C). During fine odor discrimination, gamma oscillations were significantly enhanced as compared to coarse odor discrimination. These three studies together point to a functional role for fast odor-evoked oscillations; these oscillations likely allow principal neurons in both insects and mammals to drive specific downstream neurons with small numbers of spikes.

3.3 Beta

Oscillations in the 20 Hz range are present in many cortical areas and most prominently described in the motor and olfactory systems. They were not noted in the olfactory system until experiments with waking mammals and were first seen in response to repeated presentations of a high concentration predator odor and of toluene (Heale et al., 1994; Heale and Vanderwolf, 1999; Zibrowski et al., 1998). Although some of the older olfactory literature discusses beta oscillations, this usually represents an inconsistency in terminology rather than a process different from gamma oscillations. Olfactory system beta oscillations have been noted in several types of circumstances which may or may not be related. Beta oscillations increase in response to repeated presentations of highly volatile odors in the OB and piriform cortex in waking rats (Lowry and Kay, 2007; Fig. 10). They have been observed during prestimulus periods as tuning signals for the OB from higher order areas (Kay and Freeman, 1998). Beta oscillations also increase when rats learn to associate odor discrimination with reward in operant odor discrimination tasks (Kay and Beshel, 2010; Martin et al., 2004a,b, 2007; Fig. 11). They have been noted under urethane anesthesia in rats in response to a small number of very weak odors (Neville and Haberly, 2003). Beta oscillations have also been associated with motor behavior in an olfactory reaching task, which is reminiscent of their involvement in motor tasks in other brain regions (Hermer-Vazquez et al., 2007). Coherence between olfactory areas is almost entirely in the beta frequency band, although intermittent gamma and theta coherence can be observed (Fig. 11).

3.3.1 Circuits

Little is known about the circuits involved in beta oscillations. However, beta oscillations do rely on the intact loop between the OB and other brain regions to which it is monosynaptically connected. If OB output to or input from other brain areas is blocked, beta oscillations disappear (Martin et al., 2006; Neville and Haberly, 2003). Because this is opposite the effect from that seen for gamma oscillations, where isolation of the OB from the rest of the brain increases gamma oscillations, a working hypothesis is that beta oscillations rely on connections between the OB and other parts of the olfactory system. This would predict that CSD analysis of OB activity during beta oscillations would show current events in the deep layers where most centrifugal input arrives. Only one study so far has examined beta oscillations using CSD, and in the urethane anesthetized rat beta during weak odor exposure occupies the same synaptic profile as gamma oscillations (Neville and Haberly, 2003). More study is

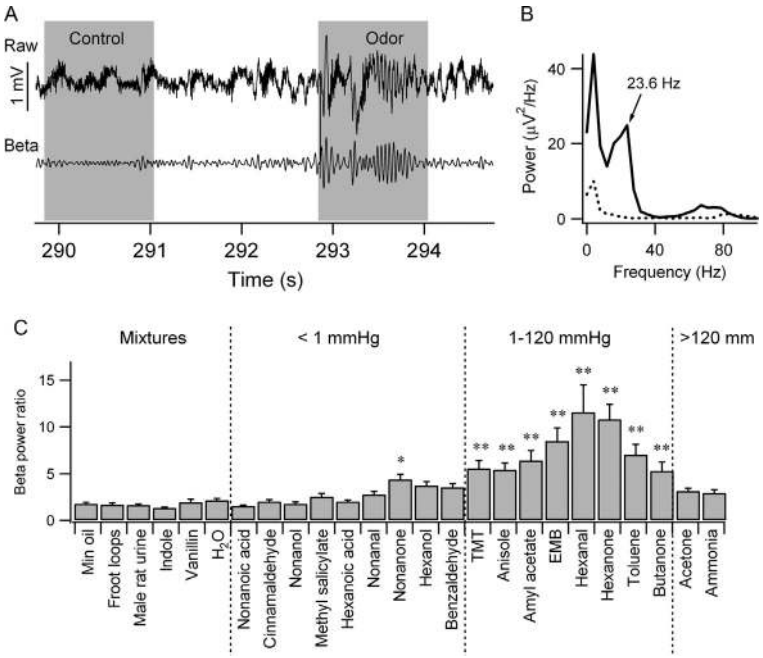

FIGURE 10

Beta oscillations increase with repeated presentations of pure high volatility odorants. (A) Sample rat OB LFP during odor presentation. Gray regions show control period (left) and odor period (right) for calculating the increase in beta power. (B) Power spectra from control and odor periods showing a large increase in beta band power. (C) Beta power increases for a large range of odorants. Mixtures are on the left and the remaining odorants are arrayed in order of increasing volatility (theoretical vapor pressure); power scale is normalized by prestimulus period, so 1 is no increase and 10 is 10 × power. Asterisks indicate significant increases from baseline ($*p<0.05$; $**p<0.01$). Note the peak increase in power in the middle of the high volatility region. At higher volatilities, beta oscillations disappear.

From Lowry and Kay (2007), used with permission.

needed in waking animals to see if beta oscillations always use the same circuit as gamma oscillations.

Another clue to the circuits associated with beta oscillations comes from the responses of waking animals to repeated presentation of pure odorants (Lowry and Kay, 2007). A sensitization effect seems to occur for highly volatile odorants, which are also very strong odorants. Are beta oscillations in this case accompanied by a stronger than normal sensory input? In our study, we found that theta band coherence at the respiratory frequency increased linearly with increasing volatility, suggesting that the effective connection between the OB and PC was stronger (Fig. 12). Because beta oscillation power drops off with even higher volatility, there may be an optimal connection strength that supports these oscillations.

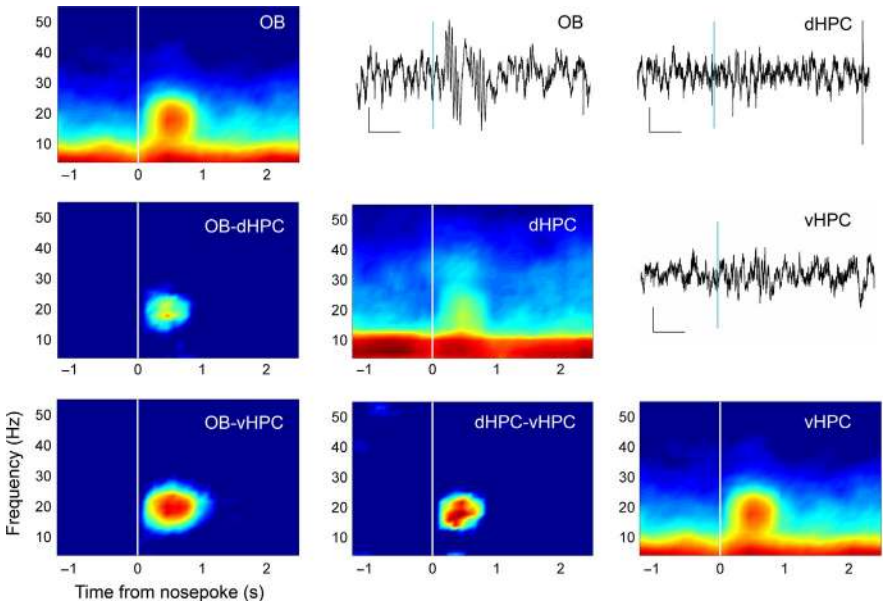

FIGURE 11

Power and coherence in the olfactory bulb and hippocampus in the beta oscillation frequency band. Data are averaged from approximately 50 CS – trials in a go/no-go odor discrimination task. Diagonal squares are averaged spectrograms in the lower part of the frequency spectrum. Time 0 (white vertical line) is the nose-poke time, which starts odor delivery. Upper off-diagonal panels show sample data all from the same trial, recorded simultaneously (scale bars: vertical—OB 0.5 mV, d/vHPC 0.2 mV; horizontal—0.5 s). Lower off-diagonal panels are coherence plots from the same set of trials represented on the diagonal (color scale: OB–vHPC 0.4–1.5 zcoh; OB–dHPC, d/vHPC 0.4–0.8). Only the beta band shows reliable coherence. dHPC: dorsal hippocampus; vHPC: ventral hippocampus.

Data originally reported in Martin et al. (2007).

3.3.2 Function

The functional role of olfactory system beta oscillations is unknown, but there are a handful of experiments that provide some clues. In motor systems, beta oscillations accompany reaching and observation of reaching movements in monkeys (Murthy and Fetz, 1996; Tkach et al., 2007). In rats performing an odor-guided reaching task, beta oscillations are coherent across motor and olfactory areas at the LFP and multiunit level (Hermer-Vazquez et al., 2007). This suggests that they coordinate activity across areas in motor tasks. However, they are also seen in humans associated with cognitive events that do not involve movement (Engel and Fries, 2010) and in the above-described rat olfactory tasks. It is possible that in the latter tasks, there is a motor involvement because beta oscillations occur late in odor sampling as rats exit the odor

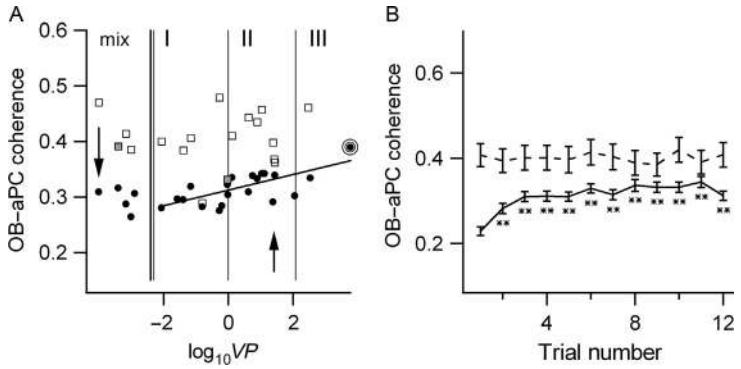

FIGURE 12

OB–PC theta band coherence during pure odorant presentation. Rats were presented with pure odorants (or mixtures) on a cotton swab. (A) Coherence versus volatility shows that in waking rats, coherence increases with increasing volatility (log *VP* – log of the theoretical vapor pressure). Open markers are from anesthetized rats, filled markers are from waking rats. (B) Coherence increases over presentations in waking rats (solid curve) but remains constant for anesthetized rats. By the third or fourth presentation, beta oscillations emerge in response to high volatility odorants in waking rats.

From Lowry and Kay (2007), used with permission.

port (Fig. 11). Beta oscillations also occur after a few presentations of a highly volatile odor, when rats transition from longer (5–10 s) to very brief odor sampling (1–2 s).

What is clear from all of these studies is that beta oscillations are highly coherent across areas in a system. Beta oscillations in the olfactory system show coherence between the hippocampus and the OB, even though there is an intervening synapse in the stellate cells of the hippocampus (Schwerdtfeger et al., 1990). They have been observed in all primary and secondary olfactory areas tested to date in circumstances that create beta oscillations in the OB. Coherence in this band may promote cooperative processing across areas, but more research is needed to move beyond correlative inferences to the causal role of beta oscillations.

4 SUMMARY AND CONCLUSION

Neural population rhythms in mammalian olfactory systems occur in discrete frequency bands that are driven by many circuits within the OB and other brain regions. Theta and beta rhythms represent processes at different ends of the cognitive spectrum, with theta primarily associated with sensory drive or respiration and beta associated with learning and experience. However, theta rhythms can be linked with learning and performance in some circumstances, and beta rhythms are linked with peripheral effects such as the strength of the input stimulus. Within mammalian

brains, theta oscillations are used in many systems to gate sensory and cognitive information. This rhythm has been extensively studied in the hippocampal and whisker systems of rodents, and there are circumstances for both systems in which the rhythms are coherent with the sniffing rhythm. Theta gating of sensory information appears to operate similarly in olfactory and thalamic circuits, so this may indeed be a common frequency band for coordinating and passing sensorimotor information within and across sensory systems. Whether the olfactory system couples with theta rhythms in other sensory and higher order systems in species that do not sniff at high frequencies is still unknown.

Faster oscillations, in the beta and gamma range, appear to be associated with sensory and cognitive processing. Beta oscillations are ubiquitous in mammalian cortical areas and show the most coherence across cortical areas. The functional role of beta is still a mystery, but it may be a mechanism for coordinating information processing across cortical areas at a faster timescale than the sensory gating of theta rhythms. In the olfactory system, beta oscillations rely on intact connections between the OB and other brain regions, which argue for their role as a system-wide coordinating mechanism. Why the frequency is the same across brain regions, individuals, and species is unknown, but may point at a universal mechanism supporting system-wide processing. Gamma rhythms present across many types of olfactory systems, in mammalian and non-mammalian vertebrates and invertebrates. In these systems, gamma varies in frequency across brain areas, individuals, and species, but relies on the synapse analogous to the reciprocal dendrodendritic synapse in the mammalian OB. Because the structure of the olfactory system appears to have evolved independently in vertebrates, insects, and mollusks, the gamma oscillation produced by the interaction between principal neurons and local interneurons may be a good solution to the high-dimensional odor-coding problem. It represents coordinated firing of many neurons across the OB and is useful for grouping spikes together in small time windows to which downstream target neurons are tuned in both rodents and insects.

There is still much to learn about the functional roles of oscillatory rhythms in the olfactory system. The more we know about what these rhythms represent in terms of underlying circuitry, the better will we be able to dissect the circuit functionally. The more we know about the behavioral circumstances in which different rhythms are enhanced or coherent with or dissociated from other areas, the better will we understand the underlying circuitry in these different behavioral states.

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