Dynamical Architecture of the Mammalian Olfactory System

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Abstract. The mammalian olfactory system shows many types of sensory and perceptual processing accompanied by oscillations at the level of the local field potential, and much is already known about the cellular and synaptic origins of these markers of coherent population activity. Complex, but chemotopic input patterns describe the qualitative similarity of odors, but animals can discriminate even very similar odorants. Coherent population activity signified by oscillations may assist the animals in discrimination of closely related odors. Manipulations to olfactory bulb centrifugal input and GABAergic circuitry can alter the degree of gamma (40-100 Hz) oscillatory coupling within the olfactory bulb, affecting animals' ability to discriminate highly overlapping odors. The demands of an odor discrimination can also enhance gamma oscillations, but this may depend on the cognitive demands of the task, with some tasks spreading the processing over many brain regions, accompanied by beta (15-30 Hz) instead of gamma oscillations.

Keywords: oscillation, gamma, beta, olfactory bulb, piriform cortex, hippocampus, synchrony, behavior.

1 Introduction

The textbook picture of sensory systems is a hierarchical one in which objective sensory input is passed to a primary sensory area, such as the thalamus or even primary sensory cortex, where some "preprocessing" happens. The processed signal is then transferred to the next cortical area where different streams of sensory information may be combined. At some level a "meaning" area adds to the signal, and the output then passes on to motor areas to produce a behavioral output. While this may seem an oversimplification to most neurophysiologists, this is the general framework that we teach our students and which biases our interpretations.

When we examine sensory processing in waking and intact animals we find that the sensory stimulus that arrives even at the first processing stage in the brain is already not objective. An individual seeks information in the environment with body movements and sensor array changes that influence what is assumed to be objective

M. Marinaro, S. Scarpetta, and Y. Yamaguchi (Eds.): Dynamic Brain, LNCS 5286, pp. 67–90, 2008.

sensory data. As a rat sniffs an odor the air in the nasal passages changes temperature and humidity. Sniffing dynamics may also direct the stimulus to optimal portions of the sensory epithelium (Schoenfeld and Cleland 2005), and head and body movements help an animal detect and locate an odor. Similar processes are at play in attentional behavior associated with any sensory stimulus. There are central mechanisms that have been discovered to accommodate for these search behaviors, such as the optokinetic effect in eye movements, but we still know relatively little about the dynamical interaction between brains and their environments.

Within the brain anatomical connections between sensory processing areas show dense bidirectional connectivity, and every sensory system shows strong effects of behavioral and arousal states that change the ways in which even very low level central neurons respond to stimulation. The olfactory system is no exception in this respect (Kay and Sherman 2007). This system also exhibits interesting dynamical behavior and has been studied from this perspective for many decades. This chapter will describe olfactory system behavioral physiology from a dynamical perspective, focusing on context-associated functional state and connectivity changes as exhibited primarily by neural oscillations.

2 Olfactory System Architecture

2.1 The Distributed Parts of the Olfactory System

The mammalian olfactory system is typically considered to be the collection of areas that receive monosynaptic input from the first cortical structure, the olfactory bulb[1]. This includes the anterior olfactory nucleus, the piriform cortex and portions of the entorhinal cortex and amygdala. However, bidirectional anatomical connections connect most parts of this system and connect the olfactory system with other systems, in particular the hippocampal system (Fig. 1).

Cortical and subcortical areas that project directly to the olfactory bulb include all parts of the olfactory system, plus areas such as the temporal pole of the hippocampus (van Groen and Wyss 1990), the septum, and the amygdala. In addition, almost every major neuromodulatory system sends output to the olfactory bulb; these include histaminergic input from the hypothalamus, serotonergic input from the Raphe nuclei, noradrenergic input from the locus coeruleus, and cholinergic input from the basal forebrain. It is commonly believed that olfactory bulb dopamine is entirely intrinsic, but in at least one species (sheep) there is a projection from the ventral tegmentum (Levy et al. 1999). Thus, the olfactory bulb receives perhaps more input from the brain than it does from the sensory receptors in the nose. All of this evidence points out that the hierarchical view of sensory processing is too simplistic, even at the anatomical level.

[1] Two reference works that give an excellent summary of olfactory system connectivity are Shepherd GM, and Greer CA. Olfactory bulb. In: The Synaptic Organization of the Brain, edited by Shepherd G. New York: Oxford University Press, 2003, p. 719. and Shipley MT, Ennis M, and Puche A. Olfactory System. In: The Rat Nervous System, edited by Paxinos G. San Diego: Academic Press, 2004.

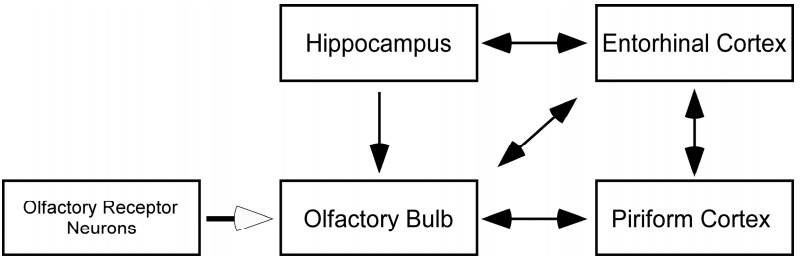

Fig. 1. The major bidirectional connections of the mammalian olfactory system. This figure illustrates that the system does not have a strictly feedforward architecture. The schematic represents brain regions and does not differentiate the different intraregional cell populations that form these connections. Not all bidirectional connections are shown.

2.2 Olfactory Bulb Input

The number of different functional olfactory receptor genes far exceeds the number of receptor types in other sensory systems, with functional genes numbering on the order of 1,000 in rodents and about 360 in humans (Buck and Axel 1991; Gilad et al. 2004; Glusman et al. 2001; Zhang and Firestein 2002). Sensory neurons in the nasal epithelium each express one type of olfactory receptor and project in an ordered fashion to the olfactory bulb. All of the sensory neurons expressing a given olfactory receptor type project their axons to a pair of identified glomeruli in the ipsilateral olfactory bulb (Fig 2) (Mombaerts et al. 1996). This makes the olfactory bulb input receptortopic, although the logic of this ordering is not well understood. This ordered input translates to a relatively high-dimensional chemotopy. However, there is also no simple logic to the chemotopy, since individual receptors expressed on sensory receptor neurons are activated by parts of molecules, with optimal activation by a few monomolecular odorants and lower levels of activation by other similar odorants. Since all molecules have multiple molecular features, a given odorant activates multiple receptor types. Thus, many odorants activate an individual glomerulus, and many glomeruli are activated by a single odorant. There is some stereotypy in monomolecular glomerular activation maps, but these maps appear to be very high dimensional (Leon and Johnson 2003). Furthermore, we have very little information regarding to which molecular features a given receptor may be most sensitive. To date, only a handful of receptors have been analyzed for optimal ligands, and only one receptor has been systematically analyzed (Araneda et al. 2000).

2.3 Basic Circuitry of the Olfactory Bulb

The olfactory bulb is a three layered paleocortical structure. The input layer is the glomerular layer, which contains principal neuron (mitral cell[2]) dendrites, glial cells and small juxtaglomerular cells which modulate sensory input and mitral cell activity (Fig 2). Juxtaglomerular cells are of many different types, but the most numerous are GABAergic, including a class of cells co-expressing GABA and dopamine. Sensory

[2] The principal neurons are actually mitral and tufted cells, which will be referred to as a group, mitral cells, in this article.

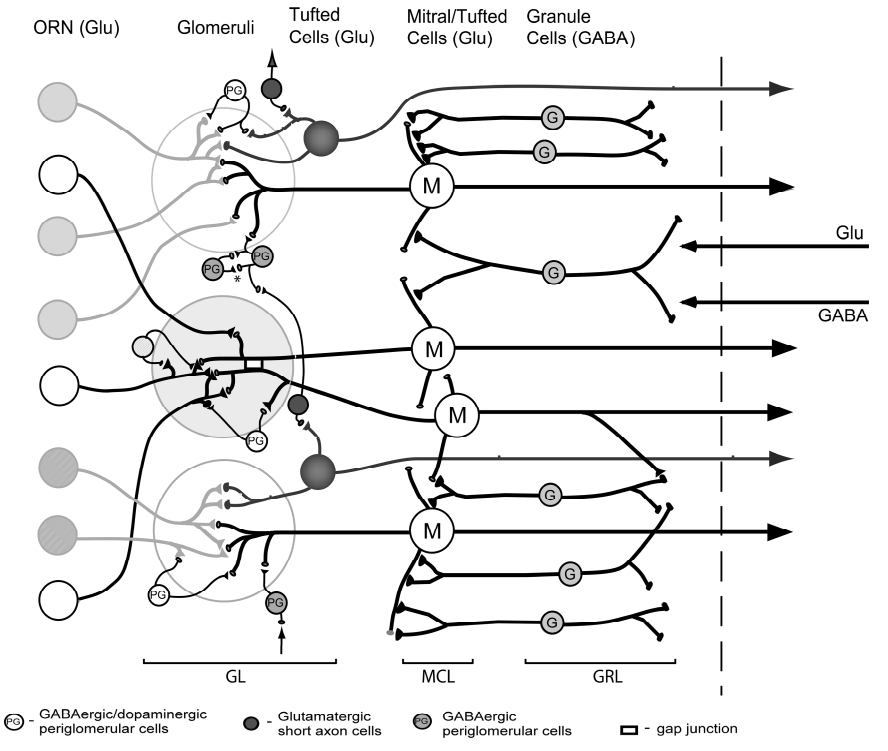

Fig. 2. Detailed schematic of the mammalian olfactory bulb circuit. Olfactory receptor neurons (ORNs) expressing the same odorant receptors send their axons to a common glomerulus in the olfactory bulb, where they synapse onto several types of cells. Shown are centrifugal GABA and glutamate projections synapsing onto lateral dendrites of granule cells, as discussed in the text. These centrifugal projections come from many brain areas and project specifically to the granular cell (GRL) and glomerular layers (GL). MCL: mitral cell layer. Dashed line indicates olfactory bulb boundary. Reprinted with permission from Kay LM, and Stopfer M. Seminars in Cell & Developmental Biology 17: 433-442, 2006.

neuron axons contact mitral cell dendrites directly in the glomeruli, and mitral cells typically have a single apical dendritic tuft in a single glomerulus, so they receive direct sensory input from only a single receptor type. (This is the only sensory system in which sensory neurons project directly to cortex, and it is one way in which substances can pass the blood-brain barrier.) Deeper layers include the mitral cell body layer about 700 μm below the pial surface, and deep to that layer is the relatively broad granule cell layer.

Mitral cells are glutamatergic and form reciprocal dendrodendritic synapses with GABAergic granule cells via their long lateral dendrites in a fiber-rich region between the glomeruli and the mitral cell layer, called the external plexiform layer. This synapse is functionally important, as it supports the gamma oscillations that are so prominent in the olfactory bulb (see Section 5.1). Because granule cells can release glutamate in a graded fashion in response to graded depolarization by mitral cells, inhibition of mitral cells can be graded, without the assistance of granule cell action

potentials, or can be pulsatile when granule cells do fire. Slice studies show that physiological levels of Mg2+ are high enough that normal activation of granule cells by mitral cells at the dendrodendritic synapse is not enough to make the cell fire but could produce a graded release of GABA (Aroniadou-Anderjaska et al. 1999).

Centrifugal input to the olfactory bulb comes in primarily onto granule cells, making contact just below the mitral cell layer in the internal plexiform layer and throughout the granule cell layer. Glutamatergic input predominates from other cortical areas and activates granule cells on their basal dendrites. Because of the density of this input onto the granule cell population, it can provide strong modulation of olfactory bulb inhibition.

2.4 Connections between the Olfactory Bulb and Other Areas

Mitral cells project their long axons onto principal neurons in other parts of the olfactory system (Fig 2). Most prominent are the projections to the anterior olfactory nucleus and the anterior piriform cortex. These two areas also project more fibers back to the olfactory bulb than other olfactory structures. Other significant projections are to the olfactory tubercle, posterior piriform cortex, taenia tecta, indusium grisium, entorhinal cortex, amygdala, and the insula (Shipley and Adamek 1984). Projections to posterior piriform cortex are sparser than to the anterior part. Projections to the entorhinal cortex are onto the layer 2 stellate cells that project directly into the dentate gyrus of the hippocampus. This makes the pathway to the hippocampus from the olfactory bulb disynaptic through the entorhinal cortex. Feedback projections to the olfactory bulb from these areas are smaller than those from the anterior piriform and anterior olfactory nucleus. The medial entorhinal cortex receives olfactory output from the hippocampus, and this area also has projections back to the olfactory bulb granule cell layer (Biella and De Curtis 2000; Insausti et al. 1997). A more direct hippocampal projection to the olfactory bulb arises from the temporal pole of the hippocampus, where a subset of excitatory cells projects directly from CA1 to the granule cell layer of the olfactory bulb (Gulyas et al. 1998; van Groen and Wyss 1990). Many other areas project to the olfactory bulb, including the amygdala, taenia tecta, septum, and substantia nigra (Levy et al. 1999).

3 Olfactory System Electrophysiology

Olfactory system activity is studied at all levels of analysis, from the genetic basis of receptor projections to the olfactory bulb, to fMRI studies of meaning related odor processing. This review will focus on extracellular methods in anesthetized and waking animals and the various types of information they convey.

3.1 Signals and Analysis Tools

The local field potential (LFP) is generally considered to be the summed synaptic activity in a local population of neurons. This often gives a rough estimate of the summed spiking activity of local cells, but this is not always the case. Many cells do not fire as frequently as they receive substantial input. In the case of the olfactory bulb granule cells, this is significant. Thus, in the olfactory bulb, the LFP is a measure

of the coherent activity of the local population, and as we will see below, this is a good estimate of the timing of mitral cell spikes. The scale of the measure is often referred to as "mesoscopic" to represent the middle level of analysis between single neurons and whole brain regions. The LFP is also a rough measure of what other brain regions receive from a given area, since the coherent activity is what survives down a pathway consisting of many axons with a distribution of conduction delays.

Analysis of LFP signals from single leads can be done with a variety of methods. Here we will concentrate on results from standard Fourier analysis. Other methods include wavelet and multitaper approaches. Both of these methods allow analysis of finer temporal structure in individual events, but all methods have weaknesses and strengths and should be chosen dependent on the question and the data. Coherence measures are often used to estimate cooperativity in a given frequency band (Chabaud et al. 1999; Fontanini and Bower 2005; Kay 2005; Kay and Freeman 1998; Lowry and Kay 2007; Martin et al. 2007). Phase estimates from these signals can be noisy and difficult to interpret and are only valid when coherence estimates are rather large. Furthermore, it is important to understand the source of the signals involved, because the absolute phase of a signal varies dependent on the position in the cortical tissue relative to the dipole field of the synaptic layer giving rise to the signal (Ferreyra Moyano et al. 1985; Freeman 1959; Martinez and Freeman 1984). To address questions of directionality in flow of these signals, some researchers are now using causal analysis methods (Bernasconi and Konig 1999; Brovelli et al. 2004; Seth 2005). These methods show great promise, particularly in a system with dense bidirectional connectivity and multiple generators of various rhythms.

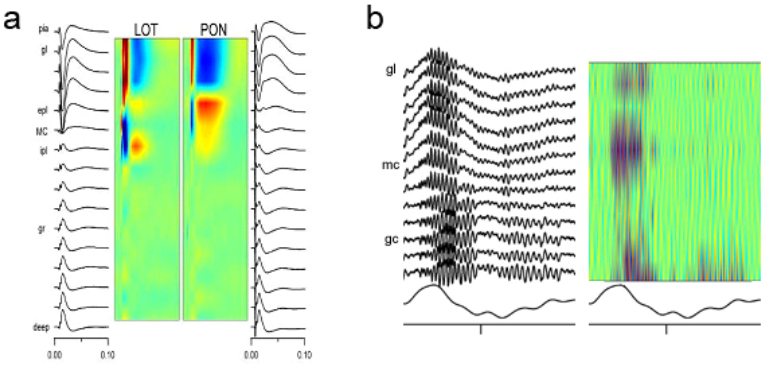

Fig. 3. Current source density profile from the olfactory bulb. **a)** Shock stimulus response in the olfactory bulb of an anesthetized rat (100 msec are shown). A shock to the lateral olfactory tract (LOT) stimulates the mitral cells antidromically and induces an oscillatory evoked potential with alternating current sinks and sources in the external plexiform layer. A shock stimulus to the primary olfactory nerve (PON) produces a similar effect, but the event begins in the more superficial glomerular layer and then activates the deeper layers of the bulb. **b)** Current source density profile in a waking rat exploring the cage. Alternating current source-sink pairs occur in the external plexiform layer and the granule cell layer. A deep source of lower frequency gamma 2 oscillation is evident in this event (Kay 2003). One second of data are shown.

Sources of oscillations can be investigated using several different methods. In waking animals a powerful tool for determining the synaptic sources of events associated with specific behavioral states is current source density (CSD). This method is a simple spatial derivative across the voltage signals recorded at successive depths perpendicular to the cortical layers. The data give a picture of the sources and sinks of current in the cortical tissue and are often displayed as color-coded spatiotemporal plots (Fig. 3a). An excellent reference paper which addresses the physics of estimating current and its sources in cortical tissue was published in 1985 (Mitzdorf 1985). This method has been used with some success in anesthetized animals (Martinez and Freeman 1984; Neville and Haberly 2003), but since many of the oscillations occur only in specific behavioral states, use of chronically implanted probes in waking animals is crucial to describing the sources of oscillations (Fig. 3b). CSD analysis has been used successfully in the hippocampus of waking rats to delineate the synaptic sources of some types of oscillations (Bragin et al. 1995; Kandel and Buzsaki 1997).

4 Coding Properties of the Input System

The anatomical structure of the input to the olfactory bulb predicts perceptual properties and neuron responsiveness to some extent. However, these properties depend in large part on an animal's behavioral state and prior experience with the stimuli.

The relatively structured input to the olfactory bulb provides some predictions about perceptual qualities of odorants. Anatomical projections from identified receptor types and glomerular activation maps are relatively stereotyped across individual animals, and this allows examination of activation pattern overlap for various odorants. Imaging studies show that odorants that are chemically similar activate overlapping regions of the glomerular sheet, while those that are dissimilar activate less overlapping regions (Grossman et al. in press; Johnson et al. 2004; Rubin and Katz 1999; Xu et al. 2003). If glomerular activation patterns represent a spatial code at the input level, then those odorants that have more overlapping patterns should smell more similar than those with less overlap, and mitral cells should respond to odorants similar to their "best" odorant.

4.1 Psychophysics

Psychophysical studies address the perceptual similarity of monomolecular odorants by several methods, and all of them rely on generalization of an odorant response to another test odorant using habituation or associative conditioning. An animal is trained to a single odorant, and probe odorants are used to test generalization of the learned response (Cleland et al. 2002). These tests verify that monomolecular odorants with larger overlap show more perceptual similarity than those with less overlap (Linster et al. 2001) (Fig. 5).

The above examples rely on generalization across a single dimension (e.g., chain length) for monomolecular stimuli. In reality, all natural odorants are blends or mixtures of many monomolecular odorants, and this makes studying them much more complicated. Even binary mixtures can have complex perceptual qualities, which have been roughly divided into two types. Elemental qualities are those in which the

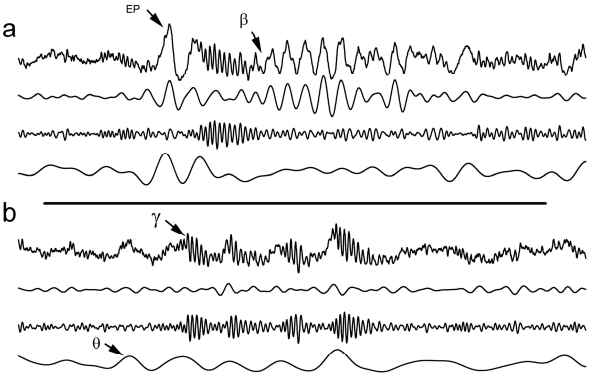

Fig. 4. Theta, beta and gamma oscillations from the olfactory bulb in waking rats. Each figure shows from top to bottom: raw data (1-475 Hz), beta band (15-35 Hz), gamma band (35-115 Hz), and theta band (1-12 Hz). 1.5 seconds of data are shown in each plot, both from the same rat in the same recording session. **a)** high amplitude beta band oscillation produced in response to odor sensitization. EP- sensory evoked potential; β- approximate beginning of beta oscillation. Note that the beta oscillation is preceded by a brief gamma frequency burst. **b)** gamma oscillations (marked by γ) associated with the transition from inhalation to exhalation during exploratory behavior. θ- marks respiratory wave in the theta band (inhalation is up). Note the relative absence of beta band activity during this episode.

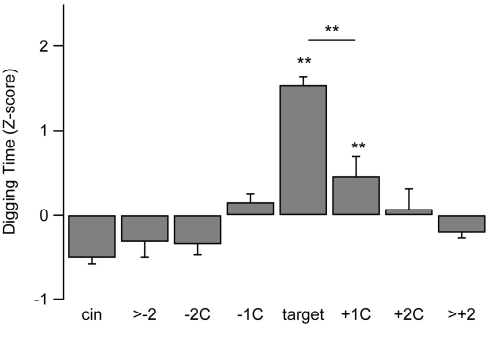

Fig. 5. Odor generalization along the dimension of carbon chain length. Mice were trained to respond by digging for an associated reward to a given aliphatic aldehyde on each day (randomly chosen 'target') over the course of ten trials. Digging times were measured in response to randomly ordered odorants in the test set, including the complete series of aldehydes (C3 – C10) and an unrelated odorant (cineole- cin). Digging times are presented as normalized Z-scores. Most mammals will generalize the association to the odorants nearest the trained odorant. The asymmetry in response is due to asymmetry in effective concentration due to differences in volatility across the odor set. There is a significant increase in response over the unrelated control (cin) for the trained aldehyde and the aldehyde one carbon longer ($p < 0.01$). There is also a significant difference between these two ($p < 0.01$).

binary mixture smells like the two components; configural (or synthetic) qualities are those in which the binary mixture smells like something different from the components. Most mixtures fall somewhere in between these two extremes, with one odorant overshadowing the other to greater or lesser extent (Kay et al. 2005). Other factors that may play a role are the physical properties of individual odorants and odorant concentrations (Kay et al. 2005; McNamara et al. 2007).

The generalization studies described above address the question "is the odorant you smell now, similar to the one which you smelled a few minutes ago?" Olfactory systems can do much more than find similarities; they are very good at finding differences. To see how the olfactory system finds differences, we turn to physiology.

4.2 Physiology

Relatively few studies have examined firing properties of olfactory bulb mitral cells in waking animals. This is because of the difficulty of isolating individual mitral cells due to their high background firing rates, packing density, and the very thin mitral cell layer. In waking rats and mice, most mitral cells show a significant modulation in firing rate associated with the respiratory cycle in which a burst of a few spikes is evoked upon inhalation (Bhalla and Bower 1997; Kay and Laurent 1999; Pager 1985). However, this is primarily during respiratory rates of less than 4 Hz. When rats transition to investigatory sniffing behavior, most mitral cells lose respiratory coupling. These two states are referred to as burst and tonic modes, representing inattentive and attentive states, respectively, by analogy with sensory thalamus neurons (Kay and Sherman 2007).

Mitral cells can respond to odor stimulation with an increase or decrease in firing rate in both anesthetized and waking animals (Bhalla and Bower 1997; Fletcher and Wilson 2003; Kay and Laurent 1999; Rinberg et al. 2006a). These neurons can also show changes in the temporal structure of firing relative to the LFP respiratory (theta) oscillation (Bhalla and Bower 1997; Pager 1983). In anesthetized rats, mice and rabbits, mitral cells show responses that suggest that they respond specifically to the chemotopic input, with nearby mitral cells responding to chemically similar odorants (Imamura et al. 1992; Katoh et al. 1993; Uchida et al. 2000). However, there is some dispute as to the generality of this receptive field response (Motokizawa 1996).

In waking rats and mice, the strongest modulation of firing rate is associated not with odor stimulation but rather the animal's behavioral state (waiting, sniffing, walking, etc.) (Fig. 6) (Kay and Laurent 1999; Rinberg et al. 2006a). These behavior-associated firing rate modulation patterns are specific to an individual neuron, are stable within a recording session and are similar across neurons recorded on the same electrode. Odor specificity, on the other hand, depends on the reward association of a particular odor. When the odor association is changed (e.g., from a positive (sucrose) to a negative (bitter taste) association) the odor selectivity of the neuron also changes (Kay and Laurent 1999). Even in anesthetized animals, a mitral cells' receptive field response can be altered by 'experience' (prolonged exposure to an odorant within the original receptive field) as has been shown for other sensory systems (Fletcher and Wilson 2003).

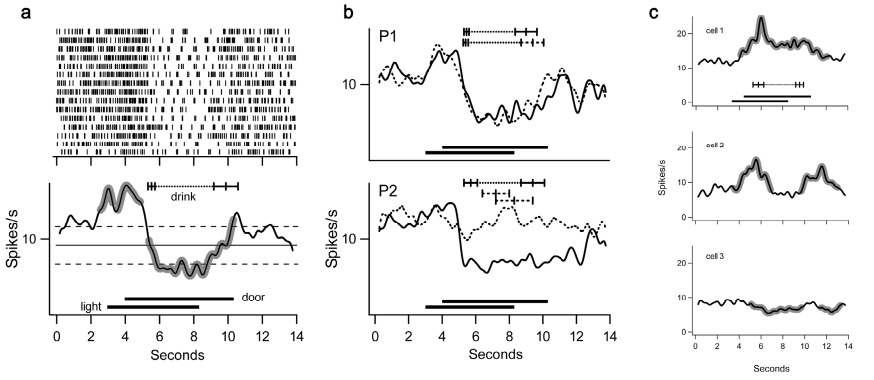

Fig. 6. Mitral cell responses are modulated by behavior. Mitral cell firing was recorded in a rat performing an odor association task: illumination of a house light signaled the opening of a door 1 second later. Behind the door was an odorant solution, which was either sweet or bitter. a) unit rasters and mitral cell firing histogram when only water and sucrose were present, with no additional odor exposure. Shading on histogram indicates time periods where firing was significantly different from the first 1 second of the trials. The horizontal line is the average firing rate before the onset of behavioral trials. Horizontal bars marked "light" and "door" signify the amount of time that the light was on and that the door was open. The bar marked "drink" shows the average onset and offset of the drinking response. b) the same neuron during subsequent odor trials. Top panel: both odors (trials randomly interleaved) were associated with a sweet solution. Bottom panel: one odor associated with the sweet solution and the other with a bitter solution. The rat ceases drinking the bitter solution in most trials (or drinks significantly later) after just a few learning trials. Note that the difference in firing rate histograms is restricted to the period in which the behavior is different. Odor selectivity responses (not shown) constitute a small but significant modulation on top of the behavioral modulation in about 10% of the neurons recorded. c) three simultaneously recorded cells that show similar background firing rates but different behavioral modulation patterns. (compiled and reprinted with permission from (Kay and Laurent 1999)).

5 Modulating the Input System

Olfactory bulb activity is strongly characterized by oscillations of the LFP, as described in section 3. The theta/respiratory oscillation is the most obvious and represents what the olfactory bulb sees of the inhalation/exhalation cycle; this also gives the neurophysiologist a tool by which to track gross olfactory behavior (sniffing rate and depth) in the LFP signal (see Fig. 4 for examples).

Initiating at the peak of inhalation is the olfactory bulb gamma oscillation, which is centered at about 70Hz in rats but can be as low as 40 Hz in cats and other larger mammals. This oscillation has been the focus of research in many laboratories since its discovery in the 1940s (Adrian 1942). Walter J. Freeman was the first to show that the gamma oscillation may play a functional role in perceptual processing. Freeman and colleagues recorded from arrays of 64 electrodes on the surface of the rabbit olfactory bulb coupled with conditioning and odor associations (Diprisco and Freeman 1985; Freeman and Schneider 1982). Several major findings resulted from these studies: 1) during odor sniffing, the frequency spectrum was dominated by power in

the gamma band, except for the low frequency respiratory rhythm; 2) the waveform of the LFP was the same on all recording leads, as measured by RMS amplitude, or PCA or FFT decomposition; 3) the spatial pattern of amplitude of this common waveform was dependent on odor association, not on the odorant itself; 4) all spatial patterns associated with baseline and odor conditions changed when the association of any odor was changed. These last two results were reflected in single unit recordings more than a decade later (Kay and Laurent 1999).

5.1 Gamma Oscillation Circuit

Within an inhalation a given mitral cell may fire only 2 or 3 spikes, while the gamma oscillation itself may show 6 or more cycles. Thus, it is clear that the gamma oscillation in the LFP does not represent periodic firing of single neurons but rather is a population effect. However, the gamma oscillation is a very good indicator of how well the local mitral cells participate in this emergent population "synchrony" with the LFP. The gamma oscillation of the LFP has been shown to be a measure of the probability that a given mitral cell will fire during a gamma burst, with the phase of mitral cell firing being 90 degrees before the peak negativity of the gamma oscillation as measured at the pial surface (Eeckman and Freeman 1990). Because the LFP is the summed extracellular field from the neighboring neurons, as the firing of mitral cells near the recording electrode becomes more precise (closer to the -90 degree mark) the gamma oscillation should become larger.

The circuit that supports the gamma oscillation is the dendrodendritic synapse between mitral and granule cells (Fig 7). A similar effect is seen in piriform cortex (Freeman 1968). The reciprocal negative feedback circuit produces a cycle of excitation of granule cells by mitral cells, inhibition of mitral cells by granule cells, disexcitation of the granule cells, and finally disinhibition of the mitral cells. A similar sequence of events is seen with electrical stimulation of the olfactory tract, which produces an oscillatory evoked potential in both the olfactory bulb and piriform cortex. This effect was the subject of two early computational models (Freeman 1964; Rall and Shepherd 1968). Since both neurons participate in this event, both show strong coupling with the oscillation, but granule cells produce a more robust extracellular field, due to their parallel and bipolar geometry.

Current source density is a useful tool for finding the synaptic origins of oscillatory events in intact animals. By computing a spatial derivative across leads (or successively deeper penetrations) evenly arrayed perpendicular to the cell layers in a cortical structure, the sources and sinks of current flow can be estimated. Current source density studies on the olfactory bulbs of intact animals show that the oscillatory component of the shock stimulus evoked potential and the spontaneous gamma oscillation map onto the dendrodendritic synapse (Martinez and Freeman 1984; Neville and Haberly 2003).

Slice studies give us further insight into the circuitry involved in gamma oscillations. While precise spiking in granule cells can be elicited by patterned stimulation (Schoppa 2006b), it is not necessary for these cells to spike in order to provide inhibition to mitral cells and support very precise gamma-coupled spiking of mitral cells (Lagier et al. 2004). Current source density has also been used on olfactory bulb slices, and the results support those done in intact animals (Aroniadou-Anderjaska et al. 1999).

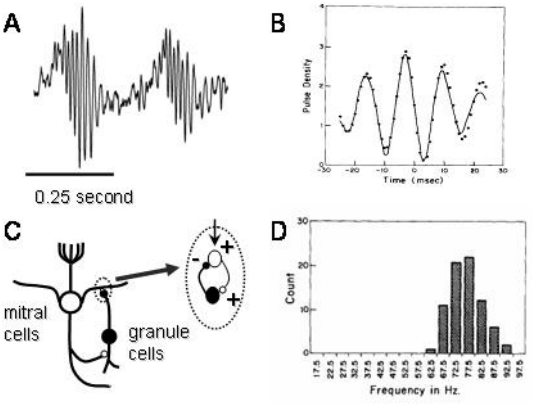

Fig. 7. Figure 7. Gamma oscillations are a network phenomenon. a) 500 msec of olfactory bulb LFP data showing two inhalations with gamma bursts. At this respiratory rate gamma bursts are common; with higher frequency sniffing, gamma bursts become irregular. **b)** The dendrodendritic synapse between mitral and granule cells appears to support the gamma oscillation, creating a local negative feedback circuit at the reciprocal synapse (Freeman 1975; Rall and Shepherd 1968). **c)** Pulse probability density (PPD) of mitral cell firing times relative to the peak of the gamma oscillation response. This is a measure of the probability of a single mitral cell firing, and the curve fit closely matches a gamma oscillation. **d)** Distribution of frequencies from many PPD curve fits. The range of frequencies matches the range of gamma oscillation frequencies. (a, c, d compiled with permission from Eeckman and Freeman 1990).

5.2 Manipulating the Circuit

Several types of manipulations to the olfactory bulb circuit result in changes to the power of gamma oscillations (Fig. 8). Removing centrifugal input to the olfactory bulb by various means results in enhancement of gamma oscillations in the olfactory bulb (Gray and Skinner 1988; Martin et al. 2004a; Martin et al. 2006). Gray and Skinner used a cryoprobe to temporarily cool the olfactory peduncle; they also recorded single unit mitral cell activity and showed that the locking to the gamma oscillation of individual mitral cells was more precise when centrifugal input was removed and gamma power was higher. This study also suggested that the gamma oscillation frequency was slightly decreased under blockade conditions. Martin and colleagues recorded olfactory bulb and piriform cortex activity during lidocaine blockade of only the feedback pathway, leaving the feedforward pathway intact (Fig. 8b). They showed that the enhanced gamma oscillations in the olfactory bulb were accompanied by somewhat enhanced gamma oscillations in the piriform cortex. Although that study did not examine the coherence of the oscillations in the two areas, other studies from intact animals show that gamma oscillations that occur simultaneously in these two highly interconnected structures can show very high levels of coherence (Kay and Freeman 1998; Lowry and Kay 2007).

Two manipulations of inhibition in this circuit produced opposite physiological and behavioral results. In the antennal lobe and mushroom body of many insects, gamma-like (20 Hz) oscillations are evoked by odorant stimulation of the antennae (Kay and

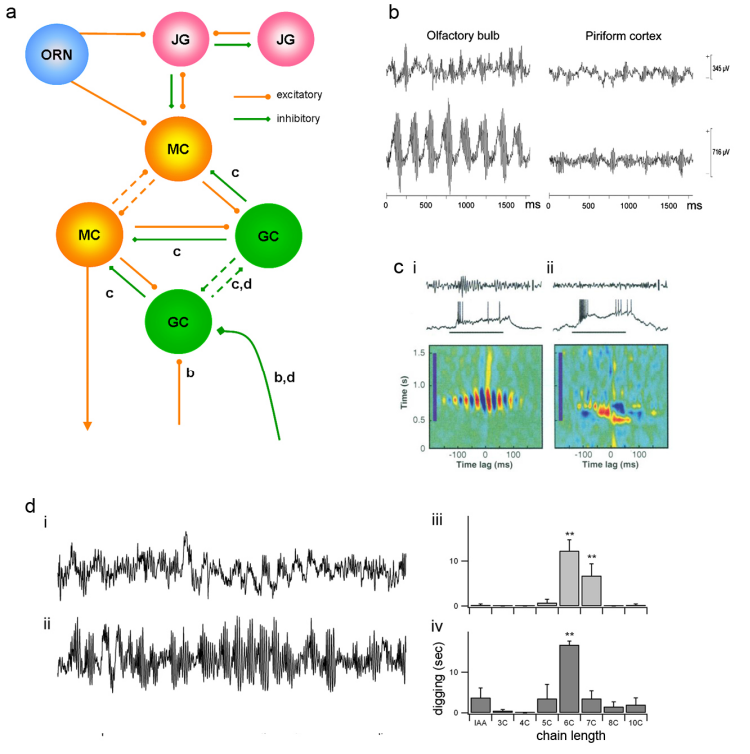

Fig. 8. Olfactory bulb circuit manipulations that affect population synchrony. a) Schematic of the olfactory bulb circuit (adapted with permission from (Freeman 1975), Academic Press). M- mitral cells, G- granule cells, JG- juxtaglomerular cells, ORN- olfactory receptor neurons. Deletions associated with manipulations in b-d are labeled with the respective letters on the schematic. **b)** Gamma activity in the olfactory bulb and piriform cortex under normal (top) and lidocaine blockade conditions (bottom). Gamma oscillations are enhanced in the olfactory bulb and piriform cortex when feedback to the olfactory bulb is blocked (reprinted with permission from (Martin et al. 2006)). **c)** odor induced 20 Hz oscillations in the locust antennal lobe (**i**: top trace and colored plot showing oscillatory correlation between unit and field responses during odor presentation). Oscillations are lost when picrotoxin, a $GABA_A$ receptor antagonist, is applied (**ii**: top trace and bottom colored plot). Middle plots- slow temporal structure of projection neuron firing is unchanged (reprinted with permission from (MacLeod and Laurent 1996)). **d)** Comparison between beta3 knockouts and littermate controls. **i)** Two seconds of LFP data the olfactory bulbs of control mice and knockouts **(ii)** during exploratory behavior. Note the obvious increase in gamma power. Control mice show normal generalization of a learned response to a similar odorant **(iii)**, while the beta3 knockouts show no generalization **(iv)** (Nusser et al. 2001).

Stopfer 2006; Laurent et al. 1996). These oscillations are supported by the reciprocal excitation and inhibition between excitatory projection neurons and GABAergic inhibitory local neurons. The projection neurons fire approximately 90 degrees from the peak of the odor-evoked oscillation, like the mitral cells in the mammalian system. Application of picrotoxin, a GABAA receptor antagonist, to the antennal lobe

removes inhibition in this circuit and abolishes odor-evoked oscillations but leaves the slower odorant responses in the spiking projection neurons intact (MacLeod and Laurent 1996) (Fig. 8c). Furthermore, downstream targets of these neurons lose their odor-selectivity when the oscillatory coupling in the antennal lobe circuit is disrupted (MacLeod et al. 1998). This same treatment applied to the antennal lobe in honeybees also disrupts oscillations, and it impairs the bees' discrimination of chemically similar but not dissimilar odorants (Stopfer et al. 1997). This is described as a deficit in "fine" odor discrimination, leaving "coarse" odor discrimination intact.

A different manipulation of GABAergic inhibition in mice produced opposite results (Nusser et al. 2001). Beta-3 knockout mice have a specific deletion of this subunit of the GABAA receptor. In the olfactory bulb this results in the specific ablation of functional GABAA receptors on granule cells, leaving other GABAergic inhibition in the bulb intact. This means that inhibition onto mitral cells at the reciprocal synapse is normal. The net effect on the circuit is to knock out mutual inhibition between granule cells and GABAergic drive to granule cells from other brain areas. This results in enhanced gamma oscillations in the olfactory bulb (Fig. 8d), and these mice are better than littermate control mice in discrimination of similar (fine) but not dissimilar (coarse) odors.

These two studies together suggest that gamma oscillation power, as a surrogate measure for neural firing precision, is related to discrimination of overlapping patterns. However, both of these treatments can cause severe disruption of other circuits, and the beta-3 knockout mice in particular have significant behavioral, anatomical and neurophysiological abnormalities (Homanics et al. 1997). What remained was proof that gamma oscillation power changes relative to the degree of overlap in the stimuli to be discriminated.

5.3 Changing the Intact Circuit with Context

It was left an open question whether or not animals can modify the amount of gamma oscillatory coupling on their own, without the aid of artificial manipulations. If the odorants to be discriminated have considerable overlap in their glomerular activation patterns (fine discrimination), more gamma oscillatory power should be seen in the olfactory bulb as compared to discriminating odorants with little overlap (coarse discrimination). In a study designed to test this hypothesis, Beshel and colleagues trained rats in a 2-alternative choice task to discriminate low or high overlap pairs of ketones and alcohols. In the case of low overlap, gamma oscillations showed a normal wide band irregular pattern during odor sniffing (Fig. 9a,b). When overlap was high and performance on the discrimination reached criterion levels, gamma oscillations were significantly enhanced (Fig. 9c).

Curiously, at the same time that olfactory bulb gamma oscillations were high, piriform cortex gamma oscillations were very low in power (Fig. 9d), contrary to what is seen during spontaneous exploratory behavior. In addition, olfactory bulb gamma oscillations did not maintain a high level once learning on an odor set reached criterion levels. Power was low at the beginning of each recording session and increased during the course of each session (Fig. 9d). These data suggest that it is not simply a wholesale increase in gamma power that accounts for enhanced odor discrimination

ability, but that the role of gamma oscillatory precision in the olfactory bulb neural population is much more complex than previously thought.

The mechanism of this dynamic change in gamma band precision is still unknown, but the phenomena described above suggest one possible scenario. The timecourse of increase in gamma power in the olfactory bulb is similar to the dynamics of a sensory-evoked gamma power increase with application of muscarinic agonists on visual cortex in anesthetized cats (Rodriguez et al. 2004). The suppression of gamma oscillations in the piriform cortex also fits a cholinergic scenario. Modeling studies suggest that acetylcholine in the piriform cortex should reduce the influence of excitatory and inhibitory neurons within the piriform cortex, thus ablating piriform cortex

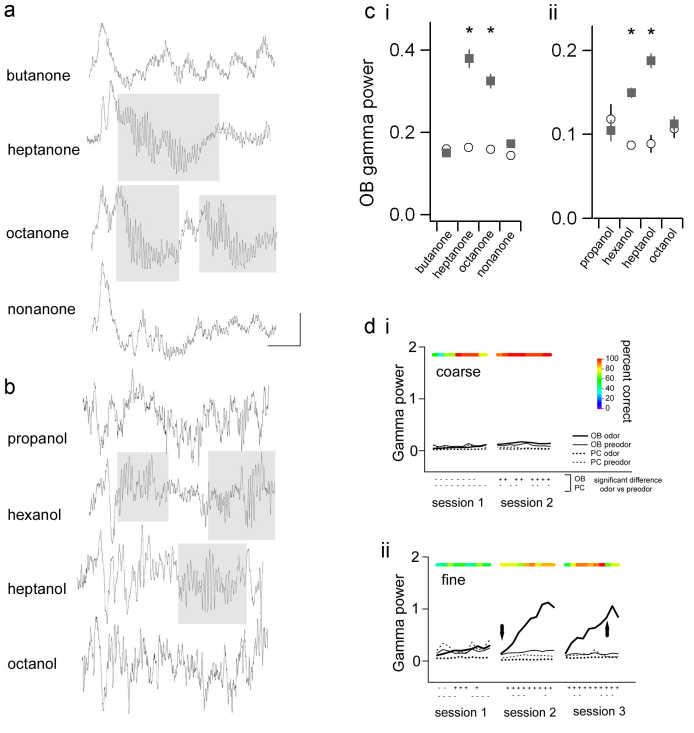

Fig. 9. Gamma oscillations are enhanced with task demand. a and **b**) Sample data for the odor sets used to test fine vs. coarse discrimination (the two center examples in **a- ketones** and **b- alcohols** are the fine odor discrimination pair, while the top and bottom in each group of 4 are the coarse pair). **c)** Olfactory bulb gamma band power distributions across 4 rats during odor sniffing for the odor sets in **a** (**c.i**) and **b** (**c.ii**). **d)** Evolution of gamma power through sessions with criterion performance throughout. **i)** Coarse discrimination shows no increase in gamma power in successive 10 trial blocks through the course of the experiment in either the olfactory bulb or piriform cortex. **ii)** Fine odor discrimination show a stead rise in gamma power only in the olfactory bulb during odor sniffing. Blockwise performance values are arrayed at the top in a color code. (compiled from (Beshel et al. 2007) and reprinted with permission).

gamma oscillations, and turning the pyramidal cells into simple input signal relays (Giocomo and Hasselmo 2007; Liljenstrom and Hasselmo 1995). The hypothesis receives some support from the increase in gamma oscillations under systemic administration of scopolamine, a cholinergic antagonist (Chabaud et al. 1999). This suggests that in the case of highly overlapping odor discrimination it is useful to maintain an 'objective' representation of the input pattern.

Other neuromodulators may also be able to modify olfactory bulb circuitry to increase or decrease gamma band cooperativity in the mitral cell population. In particular, D1 receptors at the reciprocal synapse could modify the effective inhibition from granule cells and decrease or increase precision accordingly (Brunig et al. 1999; Davila et al. 2003).

6 Multiple Functional Circuits

As described in section 3, the rat olfactory bulb also exhibits a prominent oscillation in the beta frequency band (15-30 Hz), which has been linked to odor learning, physico-chemical properties of odorants, and predator responses (Lowry and Kay 2007; Martin et al. 2007; Martin et al. 2004b; Zibrowski and Vanderwolf 1997). In anesthetized animals they are associated with the exhalation phase of the respiration and can show slightly different source-sink profiles than gamma oscillations (Buonviso et al. 2003; Neville and Haberly 2003). If gamma oscillations are the hallmark of odor associated activity in the olfactory bulb, what role do beta oscillations play? In particular, if beta oscillations are elicited upon learning odor discriminations, why aren't they evident in the task described above? This section will describe the conditions under which beta oscillations are observed, and detail the differences between beta and gamma oscillations and their behavioral correlates in the olfactory system.

6.1 Beta Oscillations and Learning

When rats learn an olfactory discrimination task in a Go/No-Go associative paradigm (response to one odor is rewarded, response to the other odor is penalized usually with a delay), enhancement of beta oscillations in the olfactory bulb and piriform cortex occurs simultaneous with the onset of correct performance in the discrimination (Martin et al. 2004b) (Fig. 10). Beta oscillations also occur in the hippocampus during odor sampling in this task, but the onset of power increase is not locked to the onset of correct performance for each odor set (Martin et al. 2007). Coherence between the olfactory bulb and hippocampus in the beta frequency band is enhanced as the rats learn to transfer the learned behavior to a new odor set, consistent with changes in the hippocampus that accompany olfactory rule learning (Zelcer et al. 2006). The coherence is maintained during odor sampling after this point. What is locked to correct performance is an enhanced coherence between the dorsal and ventral subfields of the hippocampus.

Beta oscillations involve a very large network and require intact feedback to the olfactory bulb (Martin et al. 2004a; Martin et al. 2006). When feedback to the olfactory bulb is ablated, the olfactory bulb produces only gamma oscillations during odor discrimination on the lesioned side, while the unlesioned side shows beta oscillations.

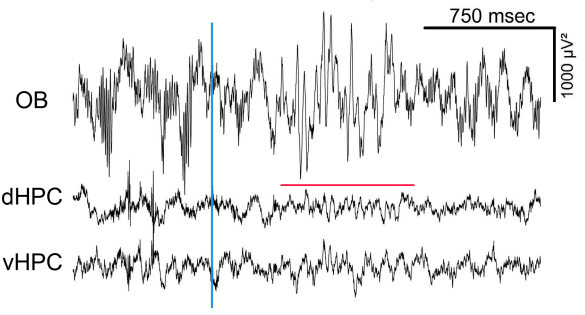

Fig. 10. Beta oscillations in the olfactory bulb are enhanced with learning in a Go/No-Go task. LFP data sample recorded simultaneously from the olfactory bulb (OB) and dorsal and ventral portions of the hippocampus (dHPC and vHPC, respectively). Blue vertical line signifies the time at which the odor was turned on, taking approximately 500 msec to arrive at the animal's nose. The horizontal red line indicates the beta oscillation. Reprinted from (Martin et al. 2007) with permission.

6.2 Olfactory Beta Oscillations in Other Conditions

Beta oscillations are also evoked using a sensitization paradigm in response to the predator odorants trimethyl thiazoline and 2-propylthietane (components of fox and weasel odors, respectively) and also to organic solvents such as toluene and xylene, absent any behavioral associative learning. The response to predator odorants resulted in the impression that these oscillations represented a specific predator response in rodents (Heale et al. 1994; Zibrowski and Vanderwolf 1997). However, we have recently argued that the volatility of these odorants may be the factor that induces beta oscillations (Lowry and Kay 2007). After 3-4 presentations of highly volatile organic chemicals (1-120 mm Hg theoretical vapor pressure), rats show prominent olfactory system beta oscillations restricted to the period of odor sniffing (Fig. 11). These oscillations are not seen in anesthetized rats under the same exposure conditions.

6.3 Differences between Oscillations and Tasks

Why are there two different types of oscillations, each elicited during odor sniffing and each associated with learning an odor discrimination? One clue may lie in the tasks themselves. In section 5.3 I detailed the study that showed that gamma oscillations are enhanced during discrimination of highly overlapping odorants. In this study, a 2-alternative choice task was used in which both odors were rewarded upon responding by pressing a lever on one side or the other (one odor was paired with the right and one with the left lever). In the behavioral studies that produced beta oscillations (section 6.1), two different types of Go/No-Go tasks were used. Two of the three studies described in sections 5.3 and 6.1 were performed in the same operant chamber with the same odorant delivery system, the same odors and the same shaping protocols (Beshel et al. 2007; Martin et al. 2007). Both tasks use the same perceptual pathway but require different response associations, pointing out the cognitive difference between the two tasks, as has been shown in human studies (Braver et al. 2001). A difference in performance accuracy and ease is also seen between 2-alternative choice

and Go/No-Go odor discrimination tasks (Abraham et al. 2004; Kay et al. 2006; Rinberg et al. 2006b; Uchida and Mainen 2003).

Go/No-Go tasks are typically easier for animals to learn and easier to transfer to new stimulus sets, and in our two studies this was indeed the case. The 2-alternative choice task requires an animal to respond with the same behavior in a different location to each of two stimuli. The Go/No-Go task requires a distinctly different behavior to be associated with each stimulus in a pair. There was little improvement in learning time from the first odor set to the last for the 2-alternative choice task (Beshel et al. 2007), while for the Go/No-Go task the number of trials required to reach criterion dropped significantly after the first training set (Martin et al. 2007).

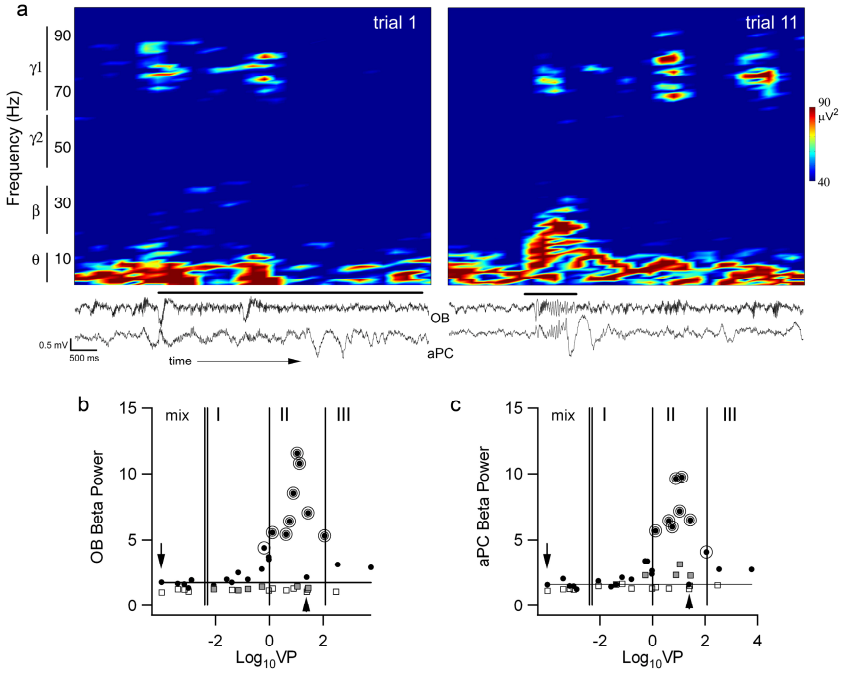

Fig. 11. Beta oscillations arise as a result of sensitization to highly volatile odorants. a) Dynamic power spectra from the olfactory bulb during a first (left) and 11th (right) odor presentation. LFP data from the olfactory bulb and piriform cortex are displayed below. The horizontal dark bar indicates the period during which the rat sniffed the odor swab. First trial investigation time is always significantly longer than subsequent trials. Note the change from gamma bursts to beta oscillations. **b)** Average olfactory bulb beta band power elicited in the olfactory bulb by odorants arrayed by volatility (theoretical vapor pressure) on a log scale. Ranges of theoretical vapor pressures are indicated (mixtures are on the far left) such that I corresponds to values below 1 mmHg, II to values between 1 and 120 mmHg, and III values above 120 mmHg. Circles around data points indicate significance values (single circle- $p<0.05$, double circle- $p<0.01$). **c)** Same as b but for piriform cortex. (Compiled and reprinted with permission from Lowry and Kay 2007).

What is different about the two systems required to produce the oscillations that is consistent with the differences in cognitive structure? The gamma oscillations produced in the 2-alternative choice task are local to the olfactory bulb, and the olfactory system appears to operate in a feed-forward fashion. The beta oscillations in the Go/No-Go task involve the entire extent of the olfactory and hippocampal systems and require a bidirectional connection between these structures and the olfactory bulb. This involvement of the downstream brain regions on primary olfactory processing may make the Go/No-Go task easier than the 2-alternative choice task. More research is needed to explain this difference.

7 Conclusion

The olfactory system presents fertile ground in which to study state-dependent dynamical neural structure. Many oscillatory states have been well-dissected, in particular the gamma oscillations, so that robust inferences can be made from population recordings. Decades of research from genetics, brain slices, and recordings in anesthetized, awake and behaving animals give us detailed information about the systems and subsystems involved in many characteristic events. New data showing changes in functional connectivity and oscillatory signature associated with task differences provide a means by which to more fully understand behavioral and cognitive influences on sensory dynamics. More research should be done to examine the sources of beta band oscillations in this system, to understand their role in learning and the relationship between learning (Martin et al. 2007) and odor sensitization (Lowry and Kay 2007). The dynamics of gamma oscillations during fine odor discrimination in the 2-alternative choice task suggest that it is not a simple binary effect that interacts with the sensory input overlap (Beshel et al. 2007). More research needs to be done to understand the mechanisms involved in the timecourse of gamma upregulation and its functional significance.

Acknowledgments

This chapter is the compilation of a set of lectures that I gave for the International School on Neural Networks, E. R. Caianiello course on The Dynamic Brain, at the Ettore Majorana Center in Erice, Italy in December 2007. I thank the organizers, Yoko Yamaguchi, Silvia Scarpetta and Maria Marinaro for the invitation, which led to many enlightening conversations. The work from my laboratory presented in this chapter is primarily from projects supported by NIDCD R01 DC007995.

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