Chapter 11
Spatiotemporal Coding in the Olfactory System

Christiane Linster and Thomas A. Cleland

Abstract Beginning in 1994, Gilles Laurent and colleagues published a series of studies describing odor-induced field potential oscillations in the locust olfactory system. While field oscillations had been described in the olfactory system previously—beginning with the work of Lord Adrian in the 1940s and including the extensive studies performed by Walter Freeman and colleagues and the later work of Gelperin and colleagues—the Laurent laboratory's work emerged at a time in which oscillations and spike synchronization in the visual system were attracting substantial attention, such that the emergence of this work triggered a renewed interest in the temporal properties of olfactory system activation and what it implied for the representation of odor stimuli.

Introduction

Beginning in 1994, Gilles Laurent and colleagues published a series of studies describing odor-induced field potential oscillations in the locust olfactory system (Laurent 1996a, b; Laurent and Davidowitz 1994; Laurent and Naraghi 1994; Laurent et al. 1996). While field oscillations had been described in the olfactory

C. Linster (✉)
Department of Neurobiology and Behavior, Computational Physiology Laboratory, Cornell University, 1 Mudd Hall, Ithaca, NY 14853, USA
e-mail: CL243@cornell.edu

T.A. Cleland
Department of Psychology, Computational Physiology Laboratory, Cornell University, Ithaca, NY, USA

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system previously—beginning with the work of Lord Adrian in the 1940s (Adrian 1942, 1950, 1957) and including the extensive studies performed by Walter Freeman and colleagues (Di Prisco and Freeman 1985; Freeman 1978, 1979a, b; Freeman and Schneider 1982; Freeman and Skarda 1985), and the later work of Gelperin and colleagues (Delaney et al. 1994; Gelperin et al. 1993; Gelperin and Tank 1990; Kleinfeld et al. 1994)—the Laurent laboratory's work emerged at a time in which oscillations and spike synchronization in the visual system were attracting substantial attention (Engel et al. 1990; Gray et al. 1990, 1992), such that the emergence of this work triggered a renewed interest in the temporal properties of olfactory system activation and what it implied for the representation of odor stimuli.

The work of Freeman and colleagues showed that odor stimulation triggers odor-specific patterns of oscillatory activity in the olfactory bulb and piriform cortex of rabbits. These evoked patterns reflected the identity (or quality) of the odorant and also were modulated by (1) the behavioral relevance of the odor to the animal, (2) the activity of neuromodulatory and feedback inputs arising from other brain areas, and (3) olfactory learning (Di Prisco and Freeman 1985; Freeman and Grajski 1987; Grajski and Freeman 1989; Gray et al. 1986, 1987). Interestingly, these results directly coincided with similar conclusions reached by other laboratories based on the odor-specific activation of characteristic populations of neurons; these odor-specific spatial patterns comprised *identity codes* in that odor quality was represented by the identities of activated neurons (Kauer 1988; Kauer et al. 1987; Lancet et al. 1982; Stewart et al. 1979). These identity codes also were found to be modulated by (1) the behavioral relevance of the odor to the animal, (2) the activity of neuromodulatory inputs to olfactory regions, and (3) olfactory learning (Coopersmith et al. 1986; Coopersmith and Leon 1986; Salcedo et al. 2005; Sullivan and Leon 1986; Sullivan et al. 1988). While continued exploration of both the identity-code ("spatial") and temporal approaches revealed substantial complexities and mechanisms of regulation, no clear division of labor between the two became apparent.

Given that both spatial and temporal activity patterns in the olfactory system exhibit specificity for odors as well as dependence on learning, experience, and behavioral state, researchers in the field have sought to determine the relationship between the two as well as the relative importance of each. Recent years have seen a substantial increase in research focusing on the relationship between dynamics, spatial activity patterns, and odor perception. A parallel line of research, mostly theoretical, has emphasized study of the cellular and network mechanisms underlying field oscillations in the olfactory system. We here review the function and mechanisms of the olfactory bulb as it is understood today, emphasizing both spatial and dynamical odor representations and the behavioral evidence pertaining to each; for reasons of space, we omit discussion of the equally important work on piriform cortex conducted by Haberly, Bower, Hasselmo, D. Wilson, and others. We conclude by reviewing recent research illustrating how dynamical and spatial activity patterns build upon one another to establish an informative and flexible code.

Olfactory Bulb Circuitry

The main olfactory bulb in rodents has been extensively described in a number of review articles (Cleland 2010; Linster and Cleland 2009) which we reiterate here briefly. Distributed patterns of activity evoked in primary olfactory sensory neurons (OSNs) by volatile chemical stimuli (odorants) are transmitted to the olfactory bulb via OSN axons. The axons of OSNs that express the same receptors, and hence exhibit the same chemoreceptive fields, converge together to form the glomeruli of the olfactory bulb input layer (Fig. 11.1a); hence, each glomerulus effectively inherits the chemoreceptive field of the OSN population that converges upon it. The olfactory bulb is believed to both filter and actively transform these incoming sensory data, performing operations such as normalization, contrast enhancement, signal-to-noise regulation, and other state-dependent operations before conveying the processed olfactory information to multiple secondary olfactory structures via the axons of mitral cells. These transformations are performed by the interaction of OSN arbors and mitral cells with multiple classes of local interneurons, notably including the periglomerular cells, external tufted cells, and superficial short-axon cells of the glomerular layer as well as the more deeply positioned granule cells, which reciprocally interact with the lateral dendrites of mitral cells (Fig. 11.1a). The olfactory bulb also receives extensive ascending inputs from other brain areas, including piriform cortex, and noradrenergic, serotonergic, and cholinergic nuclei.

Bulbar Processing of Spatial Activation Patterns

Spatially distributed neuronal activity patterns specific to individual odorants were described as early as the 1970s and are present in all species that have been investigated. Each olfactory stimulus activates a specific subset of olfactory receptor types, and hence glomeruli, that is uniquely defined by stimulus quality and concentration and can be presented as an activity map of the olfactory bulb surface (Fig. 11.1b). These bulbar activity maps have been thoroughly analyzed by Michael Leon and colleagues, who have measured the glomerular activation responses to hundreds of different odor stimuli in rats and mice and shown not only that each evokes a characteristic pattern of activity, but also that these patterns, under certain circumstances, are predictive of perceptual qualities (Cleland et al. 2002, 2007; Johnson and Leon 2007; Leon and Johnson 2003, 2006; Linster et al. 2001; Youngentob et al. 2006) (Fig. 11.1c). Similar results have been obtained by other groups using different methods or species (Carlsson et al. 2002; Galizia and Menzel 2000; Guerrieri et al. 2005; Laska and Galizia 2001; Rubin and Katz 2001).

The spatial activation patterns measured in the glomerular layer are thought to represent the average afferent activity conveyed to the glomeruli by OSNs and hence to heavily influence the activation of the postsynaptic mitral cells and glomerular interneurons that innervate each glomerulus. Any computations performed

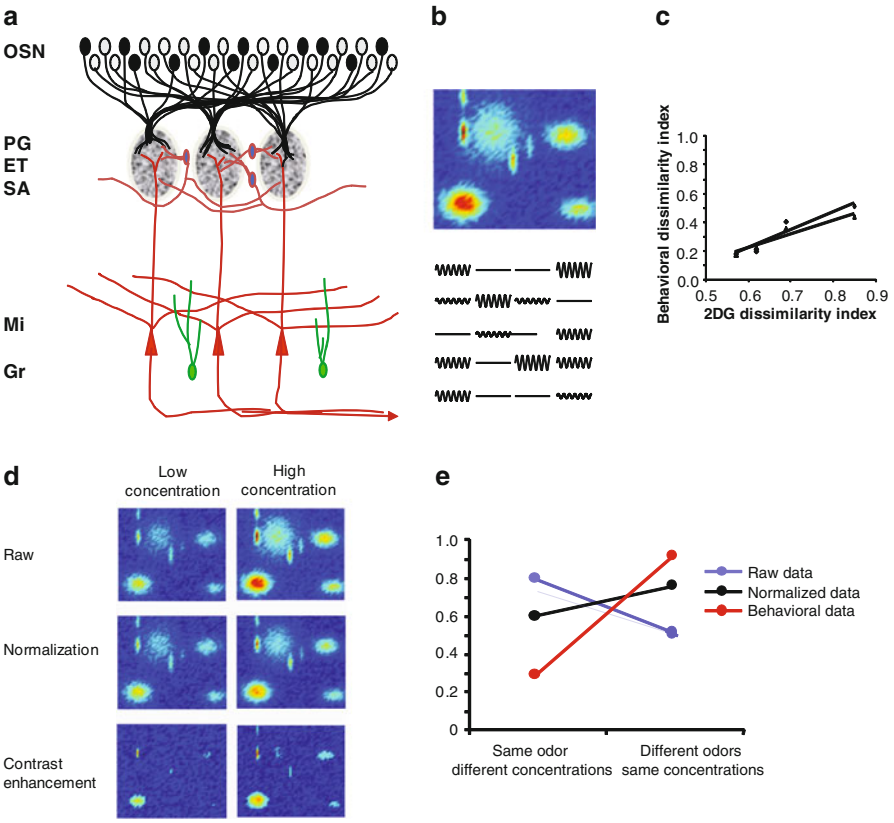

Fig. 11.1 Olfactory bulb processing. (**a**) Schematic diagram of olfactory bulb circuitry. Olfactory sensory neurons (OSNs), each exhibiting a specific receptive field for odorant stimuli, project to the olfactory bulb glomerular layer where they form excitatory synapses with mitral (Mi), external tufted (ET), and a subclass of periglomerular (PG) cells. Within the glomerular layer of the olfactory bulb, local interneurons (PG, ET, and superficial short-axon cells (SA)) interact with one another and with the principal output cells (Mi) to construct odor representations that are conveyed to the deeper layers of the olfactory bulb by Mi activity patterns. In the deeper bulb, Mi cells interact via their widespread lateral dendrites with another major class of local interneurons known as granule cells (Gr). The olfactory bulb also receives extensive inputs from other brain areas such as piriform cortex and noradrenergic, serotonergic, and cholinergic nuclei. (**b**) *Top panel.* Schematic depiction of an odor-evoked spatial activation pattern on the surface of olfactory bulb. Various methods of neuronal activity mapping, both histological (e.g., 2-deoxyglucose, c-*fos*, *Zif268*) and physiological (e.g., calcium imaging), enable visualization of the odor-specific spatial activity patterns conveyed to olfactory bulb by incoming OSNs. *Bottom panel.* Schematic illustration of odor-evoked field oscillations measured in different physical locations across olfactory bulb. The distribution of oscillatory amplitudes reflects odor quality and concentration. (**c**) Spatial activation patterns measured in the olfactory bulb glomerular layer are predictive of the perceptual similarity of odorants. Adapted from Cleland et al. (2002). (**d**) The relatively concentration-invariant representations of mitral cells are believed to be generated by computations in the OB glomerular layer that normalize incoming activation patterns (Cleland et al. 2007); other glomerular circuits perform contrast enhancement functions to decorrelate similar odor representations (Cleland and Sethupathy 2006). The figures represent odor-evoked spatial activation patterns at two different

on these spatial patterns would alter the relative activation levels of mitral cells and consequently alter the pattern of activity that is conveyed to the piriform cortex and other postbulbar structures. Indeed, the spatial activation pattern across OB mitral cells changes in response to different types of learning and has been shown to depend on the behavioral relevance of the odor stimulation (Coopersmith et al. 1986; Coopersmith and Leon 1986; Faber et al. 1999; Fernandez et al. 2009; Salcedo et al. 2005; Sullivan and Leon 1986; Sullivan et al. 1988). Mechanistically, a number of transformations have been proposed to be performed on these spatial activation patterns in the glomerular layer, including contrast enhancement and concentration invariance functions. These functions rely on interactions between mitral cells and local interneurons and, despite differences in detail, are thought to be substantially similar across species.

Concentration invariance, or normalization, of odor representations is clearly observable in the concentration profiles of mitral cells. That is, while activity in mitral cells is altered by changes in odor concentration, it does not monotonically increase with concentration as does activity in OSNs (Wellis et al. 1989) (Fig. 11.1d); indeed, on average, higher odor concentrations probably evoke slightly lower total activity levels across the mitral cell population. The network mechanism underlying this partial implementation of concentration invariance is not confirmed, though it has been proposed (Cleland et al. 2007) to rely on the deep glomerular networks of external tufted cells, superficial short-axon cells, and periglomerular cells first described by Shipley and colleagues (Aungst et al. 2003), and also likely involves feedback inhibition of OSN presynaptic arbors (McGann et al. 2005; Wachowiak et al. 2002). Notably, behavioral data collected in rats demonstrate that glomerular activation patterns normalized with respect to mean bulbar activity levels are better predictors of odor perception than raw patterns (Fig. 11.1e), as would be predicted if mitral cell activation levels were comparably normalized across the bulbar population (Cleland et al. 2007). A recent experimental study proposed a similar computational scheme in the *Drosophila* antennal lobe, concluding that relative concentration invariance is implemented in this structure as well (Olsen et al. 2010).

Contrast enhancement is a common property of sensory systems that narrows (sharpens) sensory representations by specifically inhibiting neurons on the periphery of the representation, thus enhancing the contrast between signal and

Fig. 11.1 (continued) concentrations; hot colors correspond to higher activation levels. Raw, normalized, and contrast-enhanced patterns are represented. The details of these functions and their underlying neural mechanisms have been previously reviewed (Cleland 2010; Cleland and Linster 2005; Linster and Cleland 2009). (**e**) Normalized activity patterns across OB are better predictors of odorant perceptual similarity than are raw activity patterns. The graph illustrates the pairwise perceptual dissimilarity between two different concentrations of the same odor compared to the dissimilarity between that odor and a second odor presented at the same concentration (*Behavior*), compared to the dissimilarities predicted from calculations of the overlap between their raw (*Raw*) and normalized (*Normalized*) glomerular activation patterns. The important feature is that the slopes of the *Behavior* and *Normalized* plots are both positive, in contrast to the *Raw* plot. Adapted from Cleland et al. (2007)

background (Fig. 11.1d). Contrast enhancement of spatial odor representations in the olfactory bulb is thought to be mediated by inhibitory interneurons both in the glomerular layer (*periglomerular cells*, Cleland and Sethupathy 2006; Linster and Cleland 2004, 2009; Linster and Gervais 1996; Linster and Hasselmo 1997; Linster et al. 2005)) and in the granule cell layer/external plexiform layer (*granule cells*, Arevian et al. 2008; Urban 2002; Urban and Arevian 2009)). A number of computational models have proposed solutions for this important function in the mammalian OB and insect antennal lobe, including lateral interactions between glomeruli (Linster and Gervais 1996; Linster and Hasselmo 1997), computations local to each glomerulus (Cleland and Sethupathy 2006; Cleland 2010 #50), and local and lateral interactions between mitral and granule cells (Urban and Arevian 2009).

Field Oscillations and Temporal Activity Patterns in Olfactory Bulb

In the deeper layers of the olfactory bulb, or among global interneurons in the antennal lobe, the modulation of mitral cell *spike timing and synchronization* rather than the modulation of absolute response magnitude (numbers of action potentials) is thought to be the dominant means by which interneuronal interactions affect the content of odor representations (Fig. 11.1b, *lower panel*). Degrees of synchronization among OB or antennal lobe outputs were proposed to contribute to odor processing and learning by Laurent and colleagues in a long series of studies in locust and honeybee (MacLeod et al. 1998; Stopfer et al. 2003; Stopfer and Laurent 1999; Wehr and Laurent 1999). These studies showed that the patterns of synchronization among principal neuron activation patterns, rather than the gross patterns of all odor-responsive cells, best identified specific odorants (Fig. 11.2a) and that these patterns of synchronization changed as a function of experience (Stopfer et al. 2003). Earlier studies in rabbits also had shown the odor-specificity and sensitivity to learning of dynamical activity patterns in olfactory bulb (Freeman and Schneider 1982; Gray et al. 1986), first demonstrating a potential functional role for bulbar dynamics. More recent studies have shown that olfactory bulb dynamics are modulated by behavioral demands and that behavioral performance in olfactory perceptual tasks is correlated with these dynamics (Beshel et al. 2007; Kay 2003; Kay et al. 2009; Nusser et al. 2001; Rojas-Libano and Kay 2008). For example, Nusser and colleagues showed, using genetically modified mice in which fast OB field oscillations in the gamma range were stronger than in their wild-type littermates, a robust relationship between oscillatory power and odor discrimination performance (Nusser et al. 2001). Data from Ravel and colleagues have shown that oscillations in the beta band are modulated during a behavioral experiment, strongly correlating with the animal's task performance (Martin et al. 2004a, b, 2006; Ravel et al. 2003). In these experiments, strong oscillations in the beta band (15–30 Hz) appeared in the OB field potential while the animal was first learning to discriminate between a rewarded and a non-rewarded odorant; during this same epoch,

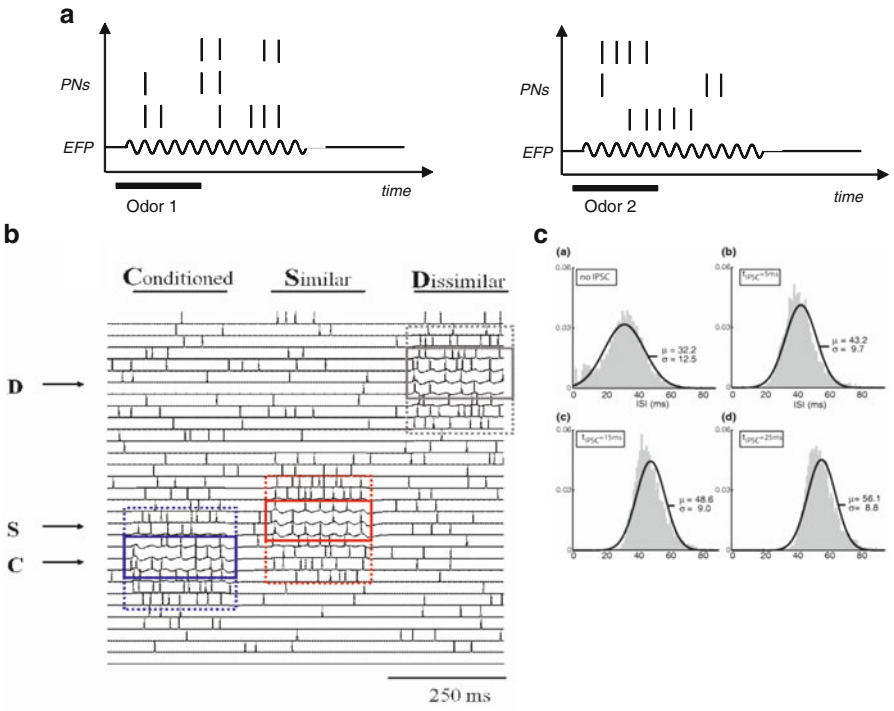

Fig. 11.2 Temporal processing of OB activation patterns. (**A**) In locusts and honeybees, patterns of synchronized spikes, rather than coarse firing rates, have been proposed to represent odor quality (Cleland 2010; Laurent and Davidowitz 1994; Wehr and Laurent 1999). In this schematic depiction, a stimulus-evoked oscillation is present in the field potential recording (*EFP*) while several projection neurons (*PNs*) fire action potentials in response to odorant presentation. While the overall PN firing rate does not enable discrimination of Odor 1 (*left panel*) and Odor 2 (*right panel*), the temporal organization of the action potentials and their synchronization patterns do enable discrimination of the two odors. (**B**) Contrast enhancement using synchronization properties. The neural responses to three odor stimuli C, S, and D are schematically depicted. Stimuli C and S evoke highly overlapping responses when coarse firing rates are used to determine their similarity (enclosed in *dotted boxes*), whereas stimuli C and D evoke very different response patterns under the same conditions. In contrast, if only synchronized action potentials are considered relevant (enclosed in *solid boxes*), the patterns evoked by stimuli C and S become nearly nonoverlapping and hence easily differentiated. While odorant D is affected in the same way, nothing is gained by the consideration of temporal information because the spatial patterns alone were already entirely nonoverlapping. (**C**) Regulation of the temporal precision of action potentials by inhibitory dendritic inputs. (**a**) Distribution of mitral cell interstimulus intervals (ISIs) under baseline conditions in the absence of incoming inhibitory postsynaptic currents (IPSCs) on the lateral dendrites. (**b–d**) Distribution of ISIs when shunting inhibitory currents were opened 5, 15, or 25 ms after a mitral cell spike. Inhibitory inputs on the lateral dendrites increased the temporal precision of mitral spiking. Adapted from David et al. (2009)

oscillations in the faster gamma band (40–80 Hz) were reduced in power. The occurrence of this phenomenon depended strongly on intact ascending projections to the olfactory bulb from other brain areas (Martin et al. 2006).

Evidence that field oscillations and spike synchronization patterns play a role in odor perception had previously been gathered in honeybees in a study showing that bees in which oscillatory dynamics and synchronization patterns were pharmacologically impaired were more prone to confuse chemically similar odorants (Stopfer et al. 1997). This study drew a lot of attention to the importance of synchronization for odor representations but said little regarding the role of spatial activation patterns. Nevertheless, by the late 1990s, the role of dynamical patterning in the olfactory bulb and antennal lobe had been widely accepted. Many laboratories began working on related questions, notably on the underlying mechanisms by which these field oscillations were generated. Presently, OB field oscillations are usually ascribed to the feedback loop between principal neurons and inhibitory interneurons (Bathellier et al. 2008; David et al. 2009; Davison et al. 2003; Lagier et al. 2004; Li and Hopfield 1989) or to intrinsic oscillatory properties of principal neurons synchronized by common inhibitory inputs (Brea et al. 2009; Ermentrout et al. 2007; Galan et al. 2006). Interestingly, to date little more has been learned about the function of these dynamical processes beyond their suggested role in further sharpening odor representations so as to improve olfactory discrimination.

Contrast enhancement by synchronization. Given that the regulation of field oscillations and mitral cell spike synchronization by dynamical interactions in the deep bulb affects perception, how might these subtle modifications of neuronal activity be interpreted by downstream structures? Theoretical models have established some mechanisms by which patterns of neuronal synchronization can be regulated by bulbar circuitry to effect arbitrary patterns of contrast enhancement and subsequently interpreted by postbulbar neurons (Cleland and Linster 2002; Linster and Cleland 2001, 2010). Interestingly, such models suggest that only spikes that are relatively synchronized with others are read out by downstream neurons, with asynchronously firing neurons effectively becoming excluded from the odor representation. This could be an important coding principle for systems in which principal neurons exhibit substantial input-independent baseline activity, as mitral cells do. Among synchronized neurons, the degree of contrast can be manipulated by changing synchronization properties (Fig. 11.2b), e.g., by changes in neuromodulatory input activity mediating attentive processes or changes in stimulus salience. Computational models using this approach have been able to explain behavioral results demonstrating that changes in synchronization properties correspond to changes in the perceptual discrimination of odors (Cleland and Linster 2002).

Signal-to-noise ratio. Muscarinic cholinergic neuromodulation, the receptors for which are expressed in the deeper layers of the OB, enhances response precision in granule and mitral cells in OB slices (Pressler et al. 2007). Simulations of mitral–granule cell interactions, in conjunction with experimental data, show that inhibitory inputs along the secondary dendrites affect spike timing in mitral cells and enhance the temporal precision of spikes occurring in response to odor stimuli (David et al. 2009) (Fig. 11.2c). While more thorough study is necessary to explore the implications, these data in conjunction suggest a role in signal-to-noise modulation for the deeper layers of bulbar processing.

Spatiotemporal Activity Patterns and Odor Perception

As reviewed above, the evidence to date clearly demonstrates that both spatial and temporal activation patterns reflect odor identity, predict perceptual qualities to a certain degree, and are modified by learning. Combined experiments in honeyebees (Stopfer et al. 1997) and rats (Beshel et al. 2007) have begun to explain their relationship to one another. In the honeybee antennal lobe, odor stimulation evokes stimulus-locked oscillations in the 15–30 Hz frequency range that are accompanied by synchronization of action potentials among output neurons (Stopfer et al. 1997) (Fig. 11.2a). Blocking fast GABAergic transmission in the antennal lobe abolished the stimulus-evoked field oscillations without evoking clearly observable changes in the odor response properties of output neurons (MacLeod and Laurent 1996). According to the Laurent group, only the synchronization properties of these neurons changed, and not their individual responses to odors. In a parallel honeybee behavioral experiment, blockade of GABAergic transmission was shown (1) to have no effect on the acquisition of an odor-reward association, (2) to have no effect on the discrimination of a chemically dissimilar odorant from the conditioned odorant, but (3) to impair the discrimination of chemically and perceptually *similar* odorants from the conditioned odorant (Stopfer et al. 1997). Subsequent calcium imaging experiments established that these chemically similar odorants evoked highly overlapping spatial patterns in the antennal lobe (Sachse and Galizia 2002). It is clear from these data that spike synchronization in olfaction becomes functionally important specifically when structurally similar odorants must be discriminated, since the perceptual discrimination of dissimilar odorants was not affected by the impairment of synchronization (Fig. 11.3).

In related work in rats, Kay and colleagues (Beshel et al. 2007) have shown that oscillatory synchrony in the olfactory bulb is systematically affected by the difficulty of an odor discrimination task. Specifically, when discriminating between highly similar odorants in a forced-choice task, the power of OB gamma oscillations was significantly increased in comparison to the oscillatory power recorded when the same rats were discriminating dissimilar odorants. These results strongly suggest that oscillatory dynamics are functionally utilized during odor discrimination in proportion to task difficulty and that behavioral demands can regulate oscillatory dynamics (Fig. 11.3). As in the honeybee experiments described above, prior knowledge and understanding of the role of odor-specific spatial activity patterns was crucial to the success of these experiments.

Together, these two data sets demonstrate that temporal dynamics and spatial activation patterns both play important roles in odor perception. Specifically, temporal properties appear to serve a secondary role, modulating and fine-tuning the basic spatial activation patterns evoked by odor stimuli in response to behavioral demands and neuromodulatory state. While much remains to be studied, the integration to date of these sophisticated mechanisms of perception has helped support

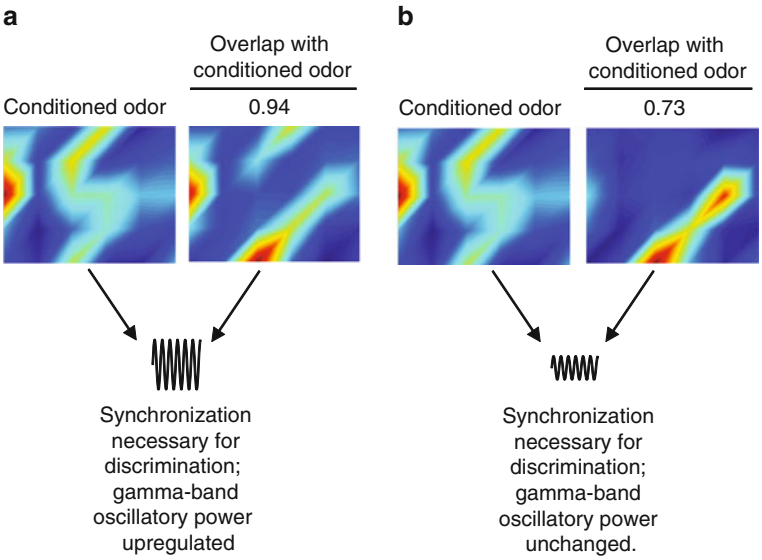

Fig. 11.3 Relationship between temporal and spatial representations of odorants. Experiments in honeybees showed that pharmacological manipulations which led to a reduction in synchrony among AL neurons also led to a reduction in perceptual odor discrimination (Stopfer et al. 1997). Specifically, this reduction in odor discrimination could only be observed in odorants that activated highly overlapping spatial representations, as schematically depicted in these color-coded images (courtesy of G. Galizia). During olfactory discrimination tasks in rats, oscillatory power in the gamma range increased when more highly similar, overlapping odorants were presented (i.e., when task difficulty was increased) (Beshel et al. 2007). Numbers above the *right panels* indicate the proportion of spatial pattern overlap with the conditioned odor (*left panels*)

a substantial revival in computational olfaction over the last 2 decades, facilitating increasingly comprehensive analyses of both spatial and temporal processing capabilities.

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