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What do electrophysiological studies tell us about processing at the olfactory bulb level?

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Abstract

Electrophysiological recordings performed in the mammalian olfactory bulb (OB) aimed at deciphering neural rules supporting neural representation of odors. In spite of a fairly large number of available data, no clear picture emerges yet in the mammalian OB. This paper summarizes some important findings and underlines the fact that difference in experimental conditions still represents a major limitation to the emergence of a synthetic view. More specifically, we examine to what extent the absence or the presence of anaesthetic influence OB neuronal responsiveness. In addition, we will see that recordings of either single cell activity or populational activity provide quite different pictures. As a result some experimental approaches provide data underlying sensory properties of OB neurons while others emphasize their capabilities of integrating incoming sensory information with attention, motivation and previous experience.

1. Introduction

In sensory physiology, primary neocortical sensory areas are defined as those receiving their input from their specific thalamic relay. This is not the case in the olfactory system in which olfactory information reaches thalamic areas after it has been processed in the olfactory bulb and the piriform cortex. Consequently, primary olfactory area cannot be defined from its connectivity. In mammals, primary olfactory receptors in the nasal cavities send their axon to an ovoid like structure, the olfactory bulb. This primitive cortical area is an obvious candidate as the primary olfactory cortex. Output cells of the olfactory bulb (mitral and tufted cells) send their axons to the widespread piriform cortex in the ventral surface of the rodent's brain. Anatomists mostly consider this area as the primary olfactory cortex (Wilson and Mainen, 2006). In this perspective, how should olfactory bulb be classified? Since there is no strict anatomical criterion for defining primary and secondary olfactory cortices one should consider their functional characteristics. From this point of view, primary cortical areas should contain output cells responding with high reproducibility to specific simple features of the stimulus and secondary areas to more complex features. For example, pyramidal cells of the primary visual and auditory areas respond to bars of a specific orientation and tones in a narrow frequency band, respectively. Secondary visual and auditory cortices are found to respond to more complex stimuli such object categories and voices. In the olfactory system, experimental demonstration of an analogous functional difference between olfactory bulb and piriform cortex would help in defining which one can be defined as the primary area. Electrophysiological recordings represent the main tool for investigating this question. Importantly, the vast majority of available data has been collected at the olfactory bulb level and much less is known at the piriform cortex level (Wilson, 2001). Due to their position in olfactory pathways and to their intrinsic organization, olfactory bulb output neurons are suspected to "extract" fundamental dimensions of the olfactory stimulus while piriform cortex plays role both in features extraction and associative memory (Haberly, 2001; Hasselmo and Bower, 1989; Litaudon et al., 1997; Mouly et al.,

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2001). In this paper we will focus on some sets of electrophysiolgical experiments aimed at identifying major functional characteristic of OB relay neurons. A good understanding of OB processing is a prerequisite for interpretation of computation at the piriform cortex level. This paper is not aimed at reviewing the whole set of available data. The main purpose is to emphasize the difficulty in integrating data collected in different experimental conditions. More specifically, we will underline the importance of two major variables: the first one is whether recordings were obtained in awake freely moving rat or from anesthetized animals. The second one is whether single cells or populational recordings were performed. As it is the case for other cortical areas, neural responsiveness has mainly been investigated through single cell recordings. Apart from the pioneer works performed by Adrian in the forties (Adrian, 1950) and later on by Freeman (Freeman, 1978; Freeman and Schneider, 1982), much less attention has been paid to populational activity collected by macroelectrodes. This type of activity can be obtained from surface electrodes (EEG) or from deeply implanted electrodes (local field potential). We will see that on one hand, data from single cells recordings in anesthetized animals reveal OB responsiveness partly compatible to the one expected from a primary sensory areas. On the other hand, data obtained from EEG, LFP recordings and single cells activity in awake behaving animals show a much more complex picture revealing characteristic found in secondary cortical areas. In addition, we will see that electrophysiological correlates of odor quality are still elusive.

2. Different recordings conditions determine the way OB is considered

In intact mammals electrophysiolgical recordings are obtained either under anesthesia or in the absence of anesthesia in restrained or freely behaving animals. These two approaches have been applied extensively in the rodent olfactory bulb. Importantly, one has to point that both spontaneous and odor-induced activity recorded in each condition are determined differently. In anesthetized animals, OB responsivess is primarily if not solely dependent on the nature of the odorant presented in front of the animal's nose and the stimulus lasts for the whole duration of presentation. Rarely animals changed their regular slow (about 1 Hz) respiratory cycle. In addition, anesthesia depresses polysynaptic activity which results in weak or no feedback exerted on the OB by more central structures. Indeed, OB receives heavy centrifugal projections originating from most of its target structures together with those belonging to major neuromodulatory systems (cholinergic, noradrenergic, serotonergic). As a consequence data emerging from electrophysiological recording under anesthesia will emphasize OB sensory properties, that is to say OB as a sensory area. In this perspective, olfactory associative areas belong to "higher" areas including those connected monosynaptically and reciprocally to the OB such as cortical amygdala and entorhinal cortex. Interpretation of data obtained under anesthesia belongs to the theoretical framework stipulating implicitly that sensory processing is almost linear from sensory areas towards high order associative areas.

On the contrary, data collected in behaving animals provide a very different picture. Neural response to odor presentation is likely to depend on changes in respiratory rhythms during sniffing (7–10 Hz) and sampling duration in the order of 1 s or less is under animal's control. In addition, neuronal response is likely to be modulated by attention, motivation and previous experience due to top down influences exerted by previously mentioned OB afferences originating from more "central" structures. Fig. 1. illustrates conceptual points of view resulting from these two approaches. In this condition identification of specific odor-induced changes in neural activity is a real challenge.

3. Some behavioral considerations

Considering that the purpose of electrophysiological studies is to decipher at least some neural correlates of odorant discrimination, these correlates would have to present a temporal dynamic compatible to the time required by animals to discriminate odors. In rodents, this question has been addressed recently by several authors (Uchida and Mainen, 2003; Abraham et al., 2004; Rinberg et al., 2006b; Ravel et al., 2003; Martin et al., 2004, 2006). In these behavioral experiments rats or mice had to sample odorants in odor port equipped with a photo beam. Depending on the nature of the odorant, animals had to make a quick appropriate decision, typically a Go or a No Go response. A Go response was associated with the delivery of a food or a fluid reward. Odorants to be discriminated were either pure chemical (ex A+ vs B) or mixture of two components which differed in relative concentration (ex Ab + vs aB). On each trial, the discrimination time was evaluated as the time of photo beam interruption in the odor port and followed by the appropriate behavioral response. One can note that this measure underestimates the real value since odorant molecules likely remain in the nasal cavities for at least a few hundred of ms following withdrawal of the nose from the odor port. Interestingly, odorant sampling duration allowing correct discrimination was found to vary from 220 to 750 ms (Uchida and Mainen, 2003, rat 220–300 ms; Abraham et al., 2004 mice 270– 490 ms; Rinberg et al., 2006b mice 275–600 ms; Ravel et al., 2003; Martin et al., 2004, 2006 rat, 530–750 ms). Different values are explained by difficulty of the task and experimental procedure. The main point is that all these experiments agree on the fact that odor discrimination is achieved in sampling duration lasting for less than 800 ms. With an average sniffing frequency in rodent in the order of 8 Hz, odor discrimination seems to be performed in about 7 cycles of 125 ms each. Consequently, what could be considered as a good candidate for electrophysiological correlates of olfactory discrimination should

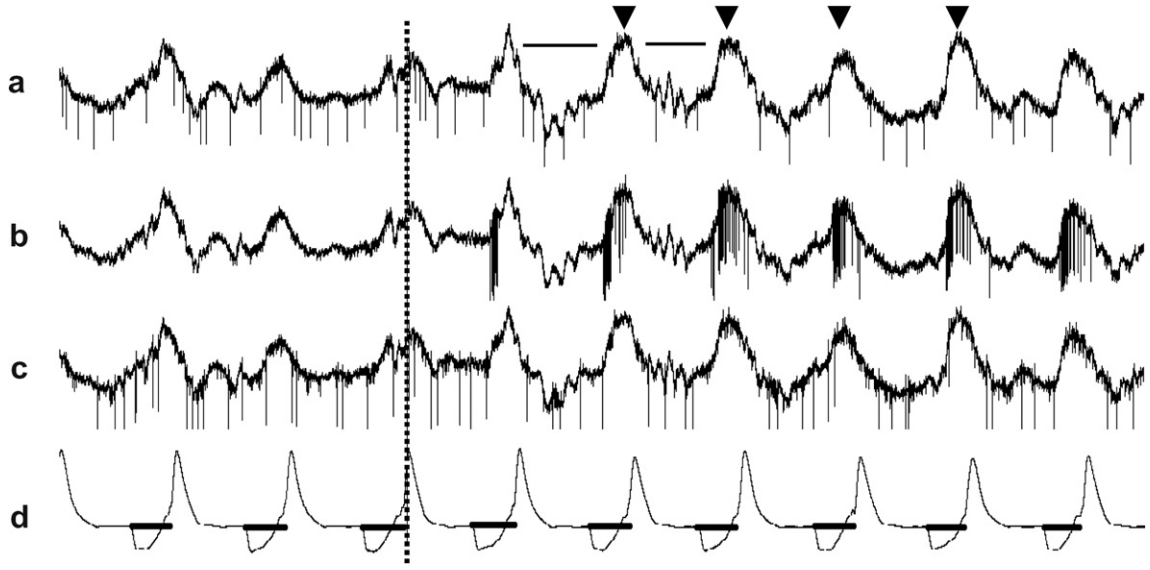

Fig. 1. Unitary and populational activity in the OB of the anaesthetized rat. a, b, c: raw signal recorded in the mitral cell layer by a multi-site electrode; a/b and b/c are separated by 50 μm. d: respiratory signal recorded by an airflow sensor placed at the nostril entrance. Inhalation epochs are marked out by thick horizontal lines, each one lasting ~500 ms. Odorant stimulation onset is indicated by the vertical dotted line. Note that mitral cell units show various temporal activity patterns: (a) shows suppression; (b) has no spontaneous activity and shows a typical bursting response, with spikes synchronized with the inspiration/expiration transition epoch; (c) also displays a respiratory-related pattern, with spikes synchronized with the expiration period. The populational activity is similar under the three recording sites. It shows large amplitude slow oscillations (~1 Hz), related to respiratory rhythm. Thin lines indicate periods of beta oscillations (~17 Hz) in the LFP activity; arrow heads point periods of gamma waves occurrence (not visible).

last for less than one second. However, this does not rule out that neural activity induced by odor presentation lasting for a longer time period would be irrelevant for information processing. Neural activity extending nose poke could be of significance for maintaining attention, short term retention and formation of associative long term memory.

4. Some neural correlates of odor representation as seen at the single unit level

Under anesthesia, a large number of experiments examined single cell (presumably mitral or tufted cells) responsiveness to odorant presentation (Buonviso et al., 2003; Chaput et al., 1992). Detailed description of such set of data can be found elsewhere (Ache and Young, 2005; Lledo et al., 2005). Here we point out some general features. First, it is worth to note that in these experiments odorants presentations are at relatively high concentration and lasted for several seconds (5–10 sec). One major observation was that, during odor presentation, single cell OB activity showed rhythmicity towards respiratory cycle (Fig. 1) Particularly during odor presentation distribution most mitral cells present a cell discharge locked to a particular moment of the inspiratory–expiratory cycle and remain fairly constant over few seconds of odor presentation. There was often no significant change in firing rate when compared to the resting activity (Chaput et al., 1992). However this cell discharge patterning was not found to be related to odor quality. Indeed, one given odorant does not induce the same temporal patterning in different mitral cells and very similar odorant molecules often induce very different patterning. The temporal organization of discharge within the respiratory cycle could enhance probability of precise synchronization between distant responding mitral cells but such evidence has not been found consistently yet. Second, most odorants can induce mitral cell response in a large OB volume. For example, amyl acetate evoked response in more than 80% of mitral cells recorded in many different locations. This suggests a widespread representation of each odorant at the OB level. Third, in our experiments most recorded mitral are broadly tuned since they respond to several different odorants whatever the chosen set of molecules. This is in contrast to what was found recently (Davison and Katz, 2007). Finally, unit reactivity in anesthetized rat was also found to be strongly modulated by previous experience. For instance 20 min exposure to one odorant in the behaving animal was found to drastically reduce the number of responding cells recorded 24 h later (Buonviso et al., 1998; Buonviso and Chaput, 2000). In summary single mitral cell recordings in anesthetized animals do not reveal the whole set of functional characteristics expected to be found in a primary sensory area. While odors induce clear change in temporal discharge within the respiratory cycle, the rules governing odor discrimination are unclear. Even though cells connected to the same glomerulus tend to share similar characteristics (Buonviso and Chaput, 1990) the type of stimulus "extraction features" they perform remains to be determined.

Interestingly, the picture emerging from single cell recordings in non-anesthetized animals is quite different. First, one has to point out that such recordings are technically challenging and the number of available data is very limited. In the experiment in which odor presentation was done to non- conditioned restrained awake rabbits, mitral cells responses present some consistency across repetition of the same odorant. Interestingly, odor presentation lasting for 5 s induced cell discharge patterned on respiratory cycle in a fashion similar to the one observed in anesthetized rat (Chaput and Holley, 1980, 1985; Chaput and Panhuber, 1982). In contrast, data obtained in freely moving animals surprisingly agree on the fact that neural correlates specifically associated to odor processing were difficult to identify. In non-conditioned rats, response to the same odorants was found to vary from one day to another (Bhalla and Bower, 1997) and to depend on behavioral outcome following presentation of familiar food odor (Pager, 1983). In animals trained in Go/No Go task less than 10% of recorded mitral cells displayed changes in firing activity during odor sampling. Most obvious changes were observed outside the period of odor sampling and were interpreted to be related to attention and contextual cues (Kay and Laurent, 1999; Rinberg et al., 2006a). In short, these experiments reveal almost no neural correlate of odor discrimination. Consequently, functional characteristics displayed by OB output cells in behaving animals are far from those expected to be found in a primary sensory cortical areas. On the contrary, neurons present characteristics of those of associative areas in which activity is related to attention, motivation, previous experience and behavioral performance. Apart from the involvement of top down mechanisms in behaving animals another variable might be of importance. This is the duration and consequently the concentration of odor sampling. While anesthetized animals are exposed for several seconds, behaving ones sample odor for less than one second, sometimes for period as short as 250 ms. This unlikely renders the identification of mitral cell patterning to respiratory cycle. When compared to several seconds exposure in experiments under anesthesia, natural sampling is likely to reduce by several fold factors the number of volatile molecules reaching neuroreceptors. This may be one reason why proportions of responding mitral cells are much lower in behaving animal than in anesthetized ones (Rinberg et al., 2006a).

5. Some neural correlates of odor representation as seen at the populational level

It is well established that olfactory structures together with limbic ones developed prominent populational oscillatory activities. This was found first at the OB level in the late forties in anesthetised hedgehog (Adrian, 1950) and described in detail later in awake restrained rabbits (Freeman, 1978). When macrolectrodes (80–100 m diameter) are positioned at the surface of the OB or deep in the structure, clear-cut oscillatory regimes are detected. Surface recordings are EEGs and deeper ones are local field potentials (LFPs). Major frequency bands of interest are the respiratory rhythm ranging from 1 to 10 Hz, the beta band (15–40 Hz) and the gamma band (60–90 Hz). Freeman's laboratory focussed exclusively on the fast Gamma activity. While recording simultaneously from 64 surface electrodes they found that maps of iso-amplitude of Gamma oscillations varied according to odor presentation and more prominently according to previous experience: habituation to the recording conditions and associative conditioning (Freeman and Schneider, 1982). Thus, in these experiments characteristics of the Gamma activity parallel what was found later on with single unit recording in behaving animals.

More recently, our group performed a series of experiments in which LFPs were recorded from several sites in the OB and piriform cortex while rats were engaged in a Go No go discrimination olfactory task (Ravel et al., 2003; Martin et al., 2004, 2006). Main findings were the following. When rats were not actively sampling odor in the odor port, ''ongoing'' oscillatory activity was dominated by the respiratory rhythm and by the fast Gamma activity which appeared in puff at each inspiration (Fig. 2). When the animal briefly nose poked (for less than 1 s) for odor sampling, ongoing activity was markedly modified and response was greatly modulated by the level of training. In naïve animals, there was a clear reduction in Gamma band oscillations and the emergence of a much slower one found to be in the beta band (Fig. 2). In naïve animals the amplitude of the beta oscillation was low on each trial but changes were found significant over many trials. After several days of training rats learned that one odorant was paired with a reward (sucrose solution, Go response) and another one paired with nothing or punishment (bitter quinine solution). Emergence of clear-cut No Go response following non-reinforced stimuli was correlated with the appearance of large beta oscillations locked to the period of odor sampling. The dominant frequency of the oscillation was near 27 Hz. (Fig. 2). In addition, it was found that this beta oscillatory response presents the following characteristics: its amplitude, latency and spatial distribution into the OB depend on the nature of the odorant; the gain in amplitude over days was correlated with the emergence of the correct behavioural response for reinforced, non-reinforced and punished odorants; the beta oscillation lasted from 200 to 500 ms and appears as soon as 200 ms after initiation of nose poking; emergence of the beta oscillation at the OB level required interaction with more central structures presumably the piriform cortex (Neville and Haberly, 2003; Martin et al., 2006). So, the dynamic of the beta response fits well with behavioural data which determined average duration of sampling for successful discrimination. In summary, the beta response is odor-induced and its latency, amplitude and duration are modulated by associative conditioning. It is interpreted as a possible neural correlate of olfactory discrimination in

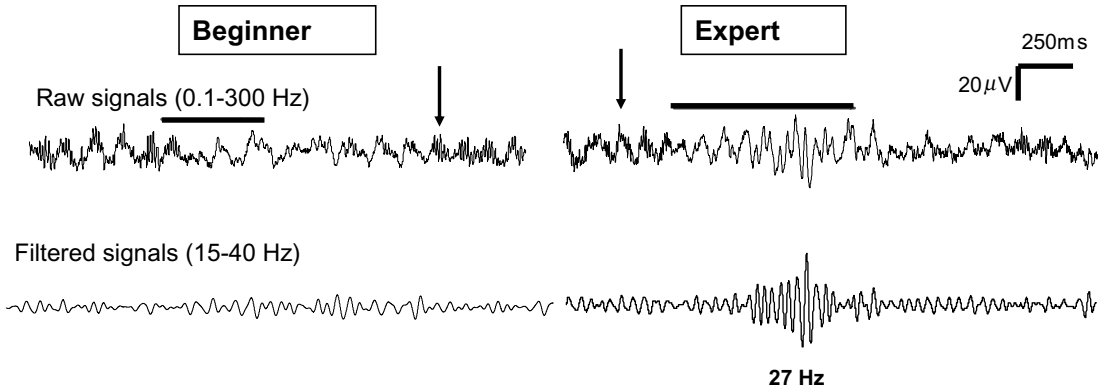

Fig. 2. Typical examples of LFP signal recorded close to mitral cell layer in the OB of a behaving rat. The rat is engaged in a two odor Go/No Go task in which odor sampling is done during nose poking at the odor port. The same signal was obtained at the beginning of training (beginner, left) and several days later after the animal has learned the task (expert). Upper part: raw signal filtered 0,1–300 Hz); lower part: filtered signal 15–40 Hz. Slow fluctuations reflect the respiratory rhythm and fast Gamma oscillations occur on top of each inspiration during spontaneous activity (vertical arrow). Brief odor sampling is associated with strong depression of Gamma activity and emergence of slower oscillations found to be in the beta range (15–40). In naive animals, amplitude of the beta response is weak but one can see its large amplitude in the expert condition. In this situation the beta oscillation is centered on 27 Hz and restricted to the duration of odor sampling.

non-restrained and non-anesthetised animals. Cellular and ionic mechanisms supporting abrupt changes from the Gamma regime to the beta regimes are unclear. However, the role of GABAergic inhibition is likely. Indeed, GABAergic inhibition was found to play a critical role in fast Gamma oscillations at the olfactory bulb level (Lagier et al., 2004, 2007; Nusser et al., 2001). Since we found that transient or permanent deafferentation of the OB from the rest of the brain drastically enhanced amplitude of ongoing Gamma oscillations and suppressed odor-induced beta oscillation (Martin et al., 2006) the switch is likely determined by the strength of action of centrifugal projections exerted on bulbar GABA interneurons. Brief olfactory sampling in motivated and aroused animal is likely to be associated with a transient attenuation of inhibition at the level of dendro-dendritic synapses, allowing emergence of slower beta oscillation. Interestingly, increasing depolarization in bulbar mitral cell neurons triggers the burst of synchronized action potentials together with beta band membrane oscillations. (Desmaisons et al., 1999). Different level of GABAa type inhibition in awake and anesthetized animals (Rudolph and Antkowiak, 2004) could also well-explain the differences in expression of Gamma oscillations in these two recording conditions.

It is thus tempting to reconciliate data from single cell recordings and those from LFPs recordings. However this is not an easy task. Although recording of both kinds of signals is feasible in anesthetised rats (Buonviso et al., 2003, see Fig. 1) there is no available data yet in behaving animals. Second, although origin of LFP signals is controversial, they likely reflect currents mainly generated at synaptic level. In the OB, this corresponds to numerous reciprocal dendrodendritic synapses within the external plexiform layer. Spiking activities recorded with the type of electrode used most likely originate from mitral and tufted cell bodies. So one has to understand functional relationship between dendritic LFP activities and spiking somatic activities. In addition, although the anesthetised preparation reveals clear-cut patterning of spiking activity relative to the slow respiratory rhythm (Fig. 1), the expression of Gamma and beta oscillations is different to what is seen in freely moving rat. Indeed, under anaesthesia, we found no ongoing Gamma oscillations, while odor presentation induced alternated puffs of Gamma and beta oscillation (Buonviso et al., 2003). This contrasts with what was found in freely behaving rat in which Gamma oscillations dominated spontaneous activity, depressed during odor sampling together with emergence of the beta oscillation (Ravel et al., 2003; Martin et al., 2004, 2006). This is to say that a detailed description of LFPs/spiking relationship could be different in anesthetised and non-anesthetised preparations.

6. Concluding remarks

As already pointed out (Rinberg et al., 2006a; Rinberg and Gelperin, 2006), electrophysiological correlates of neural representation at the OB level markedly differed according to two major variables: anaesthesia vs awake behaving animals and the type of recordings (single cell vs populational). Data obtained in these different conditions are hardly reconcilable. This difficulty emerges for at least two reasons. First, at the OB level, each odorant seems so to be represented by widespread neural assemblies. Identification of neural correlate of such representation at single cell level likely requires simultaneous recordings of several units over a large OB volume. This is technically challenging mainly in freely behaving rodents. Second, we still have poor understanding on the relationship between single mitral cell spiking activity and populational oscillatory activity. For instance, does the beta response during odor sampling associated with detectable change in mitral cell temporal activity? Changes in unit activity can be expressed either in terms of synchrony, firing rate or

reorganisation of temporal discharge within slow and fast periodic phenomenon. Preliminary experiments have started to examine this question in urethane anesthetized rats (Buonviso et al., 2003, 2006).

A great deal of effort has been carried out in characterising what is going on in the mammalian OB but fundamental questions are unresolved. Apart from the well-established spatial dimension of the neural representation of odors (Wilson and Mainen, 2006) the neural dynamic supporting olfactory discrimination in a few hundred ms time period is still elusive. Finally, neurons in the OB are clearly under influence of many other brain structures and are integral to the circuit supporting olfactory memory and possibly multimodal integration as suggested in neocortical areas (Ghazanfar and Schroeder, 2006). This is why the identification of bulbar sensory and associative neural properties is challenging.

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